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CORONARY SCLEROSIS

AN ANALYSIS OF NINE HUNDRED TWENTY-EIGHT CASES

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THERE are three conditions frequently associated with angina and sudden death which have to be considered in a study of deaths due to coronary insufficiency. These are aortic stenosis, syphilitic aortitis, and atherosclerosis of the coronary arteries (coronary sclerosis).

About 15 per cent of individuals with aortic stenosis severe enough to cause death die suddenly, and angina is common. The cause of the angina and sudden death in these cases is still a debated question. All theories so far offered to explain the cause assume a coronary insufficiency.

More than 20 per cent of patients with syphilitic aortitis die more or less suddenly, and angina and sudden death are also common in this group. The cause of the angina and sudden death is obvious. The orifices of the coronary arteries are narrowed by intimal thickening of the aorta.

The most common cause of angina and cardiac sudden death, however, is coronary sclerosis of atherosclerotic type with or without coronary thrombosis and infarction. It is with a study of this group that this paper deals.

No attempt is made to review the literature on coronary disease because this has recently been well done by Levy[1] and his coauthors in "Diseases of the Coronary Arteries and Cardiac Pain."

MATERIAL

The cases studied were all autopsy cases and were described in the records of the department of pathology at the University of Minnesota during the years 1910 to 1936, inclusive. Many of the hearts have been restudied. In others the records had to be relied upon, as the hearts had not been preserved. All histologic ma-

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terial was restudied. There were 928 cases for study, but information on the various conditions analyzed was not always available in all cases; hence some of the tables contain less than the total number.

INCIDENCE

White[2] has observed that coronary sclerosis as a cause of heart disease varies somewhat in its relative incidence in different parts of the world, largely according to the frequency of such other causes as rheumatic heart disease, hypertension, and syphilitic aortitis. He also emphasized the necessity of stating whether we refer to coronary sclerosis of a degree severe enough to cause death or just to the presence of atherosclerosis in the coronary arteries. The latter condition is present in a high percentage of persons, especially in those 40, or more, years old.

In all of the cases included in this study there was severe involvement of the coronary arteries, and death was considered as being due primarily to coronary disease.

The 928 cases in our series constituted 24 per cent of the 3,872 cases of death from noncongenital cardiac disease that occurred in 23,972 autopsies (4 per cent of all deaths in patients above 6 months of age, and 6 per cent of all deaths of patients 40 years old, and above). Since heart disease is the most common cause of death, the importance of coronary sclerosis becomes evident. Dublin[3] believes that the incidence of death from coronary disease is increasing.

CLASSIFICATION

On a clinical basis Levy classified patients with coronary sclerosis into five groups: (1) those with no symptoms and sometimes without signs, the latent group; (2) those with congestive heart failure; (3) those with cardiac pain; (4) those with digestive disturbances; and (5) those with thrombosis.

We placed our autopsied patients in two groups: (1) those with hypertension and (2) those without hypertension. The first corresponded in general to Levy's second group, those with congestive heart failure. These included most of the hospitalized patients. Our second group, or those for the most part without hypertension, corresponded in general with Levy's first group, the latent group, or those with no symptoms or signs. Cases which belong in this second class are more frequently seen by the pathologists than by the internists. This type of sudden cardiac death is commonly seen in a coroner's service. These two groups (those with hypertension and those without hypertension) are further analyzed in respect to etiology, outstanding clinical characteristics, and pathologic findings.

ETIOLOGY

The primary exciting cause of coronary sclerosis cannot be stated until the cause of arteriosclerosis is understood. This is far from being known at the present time.

Age.—Coronary sclerosis may be present at a very early age, even as early as a few weeks, but the degree of sclerosis referred to in this discussion is rarely found under 30 years and most of the patients are much older. Table I gives an analysis of 923 cases in regard to age. The greatest number of patients died in the fifth, sixth, seventh, and eighth decades; only six died in the third decade. The youngest was 22 years old. The ages of those in the nonhypertensive group were scattered over a greater range (fourth to ninth decades). The disease is definitely one of adults.

TABLE I

AGES AND SEX OF PEOPLE DYING WITH CORONARY SCLEROSIS (923 CASES)

DECADES	WITH HYPERTENSION				WITHOUT HYPERTENSION			
	MALES		FEMALES		MALES		FEMALES	
3	1	0.2%	0	0%	5	1%	0	0%
4	7	1.5	1	0.2	33	6.5	1	0.2
5	46	11.0	7	1.5	80	15.5	7	1.5
6	85	20.5	18	4.5	135	26.5	16	3.0
7	111	27.0	39	9.5	116	22.5	24	5.0
8	62	15.0	20	5.0	58	11.0	10	2.0
9	14	3.0	3	1.0	14	3.0	9	1.5
10		0.0		0.0	1	0.2		0.0
	326	78.2	88	21.7	442	86.2	67	13.2

Sex.—Males are regularly regarded as being more commonly afflicted with coronary sclerosis than females. In our series of 923 cases (Table I) there were 768 males and 155 females, a ratio of nearly 4.9 to 1. This, however, is not the ratio in the entire population in Minnesota, for in our material in these decades the ratio of males to females coming to autopsy is 2 to 1. As corrected, our ratio of males to females should be 768 to 310, or about 2.5 to 1. It is evident that death from coronary sclerosis must be expected in females.

Hypertension is the most common suggestive etiologic factor in coronary sclerosis. On the other hand, coronary sclerosis of severe grade is frequently seen without any evidence of hypertension. In our study two criteria were used for determining the existence of hypertension: (1) a history of high blood pressure, and (2) cardiac hypertrophy in the absence of valve defect or any other known cause of hypertrophy. Heart weights of 500 gm., or more, in males and 450 gm., or more, in females were the minimum weights regarded as indicating that hypertension had existed. Hearts with weights slightly below these figures probably were also hypertensive hearts, but were not classed as such in this study.

By using these criteria it was found (Table II) that 418 (45 per cent) of the 928 patients with coronary sclerosis had hypertension; 510 (55 per cent) were placed in the nonhypertensive group. But it is quite evident from the weight of the hearts that many in the latter group also probably had hypertension. In 224 of these 510 the hearts

of the males weighed 400 gm., or more, and of the females 350 gm., or more. Considering these as probable hypertensive cases the number of patients with hypertension is raised to 642, or 69 per cent of the entire group of 928. This incidence of hypertension with coronary sclerosis (69 per cent) is practically the same as was previously estimated from another series by a study of heart weights and the presence of arteriolosclerosis in the kidneys.[4] This high incidence of hypertension with coronary disease appears to be more than a coincidental finding.

TABLE II

FREQUENCY OF HYPERTENSION WITH CORONARY SCLEROSIS (928 CASES)

History, plus, or heart weights 500 gm. or more in males (202) and 450 gm. or more in females (216)	History, minus, or absent with heart weights below 500 gm. in males and 450 gm. in females
418—45 per cent	510—55 per cent
History, plus, or heart weights 400 gm. or more in males and 350 gm. or more in females	History, minus, or absent with heart weights below 400 gm. in males and 350 gm. in females
642—69 per cent	286—31 per cent

CLINICAL CHARACTERISTICS

The clinical considerations noted were duration of symptoms, pain, conditions under which death occurred (effort, rest, etc.) and dyspnea.

Duration.—Adequate histories on duration of symptoms were recorded in 877 of the 928 cases. The duration of symptoms was compared in the hypertensive and nonhypertensive groups. Table III shows the durations as divided into four groups in respect to time: (1) those who died suddenly or who had symptoms lasting but a few minutes; (2) those with symptoms lasting from one hour to one month; (3) those with symptoms lasting from one month to one year; and (4) those who had symptoms lasting from one year to five years, or more.

TABLE III

DURATION OF CLINICAL COURSE IN CORONARY SCLEROSIS (877 CASES)

DURATION	WITH HYPERTENSION		WITHOUT HYPERTENSION		TOTAL	
Sudden to few minutes	52	13.0%	196	41.0%	248	28%
1 hour to 1 month	91	22.5	117	24.5	208	24
1 month to 1 year	108	26.5	73	15.5	181	20.5
1 year to 5 or more years	151	37.5	89	18.5	240	27
	402	99.5	475	99.5	877	99.5

In the first group (those dying suddenly or in a very short time) the manner of death was described by the following terms: "dropped dead," "fell dead," "found dead," and "died in a few minutes." Thirteen per cent of the 402 in the hypertensive group and 41 per cent of the 475 in the group without hypertension were found to have died somewhat suddenly. The frequency of sudden death was considerably greater in

the nonhypertensive group. The number of sudden deaths among those dying in from one hour to one month was about the same in the two groups. As the duration of symptoms increased from one month to one year the percentage ratio of the hypertensive group to the nonhypertensive increased to 26.5 to 15.5. Of those having symptoms from one year to 5 or more years, 37.5 per cent were in the hypertensive group and 18.5 per cent in the nonhypertensive group. It would appear that people dying of coronary sclerosis associated with hypertension tend to have symptoms for a longer time than those without hypertension. In fact, nearly one-half of those without hypertension had no recorded histories.

Pain was the most common symptom recorded. It was localized in different places: heart, chest, precordium, substernal region, epigastrium, abdomen, gallbladder region, retrosternal region, shoulders, gastric area, between the scapulas, back, throat, and posterior part of neck. The pain was described as being referred to shoulders, arms, hands and fingers, hips, legs, elbows, and jaws. It was characterized by the following terms: "cardiac," "tightness in chest," "pressure in chest," "sharp," "cramplike," "viselike," "shooting," "choking," "asthmatic," "constrictive in chest," "numbness," "knifelike," "gastric disturbance," "indigestion," etc.

Pain was recorded as being present in the group with hypertension in 60 per cent of the cases, and absent in 3 per cent (Table IV). No mention of pain was made in 37 per cent. In the group without hypertension, pain was recorded as present in 49 per cent, absent in 1 per cent, and not mentioned in 50 per cent. In the entire number of 928 cases pain was recorded as present in 54 per cent, absent in 2 per cent and not mentioned in 44 per cent. There was a record of pain in more than 50 per cent. It is quite likely that it was present in a larger number, but not recorded. Many of the patients, especially in the nonhypertensive group, died suddenly without any recorded histories.

TABLE IV

FREQUENCY OF PAIN WITH CORONARY SCLEROSIS (928 CASES)

PAIN	WITH HYPERTENSION		WITHOUT HYPERTENSION		TOTAL	
Present	250	60%	251	49%	501	54%
Absent	12	3	6	1	18	2
Not mentioned	156	37	253	50	409	44
Total	418	100	510	100	928	100

Pain was the most constant symptom, but other complaints were of dyspnea and edema, fainting, dizziness, paralysis, gastric distress, symptoms resembling disease of the gallbladder, asthma, rheumatism, etc.

Conditions Under Which Death Occurred.—The way in which death occurred has much importance, especially from a medicolegal point of view. Many terms were used to explain how death occurred in our

cases. The following were some of the most common ones: "fell dead," "dropped dead," "found dead in, going to, or coming from the bathroom," "died suddenly while walking, at work, at home, in hospital, in bed, in automobile, on train, on street, on way to hospital, sitting in a chair, waiting in line for pay check, after putting out washing, putting up stove, following sneezing, on golf course, while digging ditch, in restaurant, running an elevator, after changing an automobile tire, running to catch a streetcar, at a wrestling bout, emptying waste, after struggle, packing for a trip, tripping on rug, picking flowers, in chiropractor's chair, in barber's chair, after eating his wedding dinner, under tree during thunder shower, on way to doctor's office, while delivering a speech, upon receiving a bouquet of flowers from her husband." Many other terms were used, but the foregoing include those relating to effort, rest, emotion, etc.

In analyzing these cases the conditions under which death occurred were placed in the following groups: (1) effort (work, play, other effort); (2) rest (in hospital, at home, in room, in bed, and other rest); and (3) miscellaneous (bathroom, found dead or died suddenly, while eating, with excitement). Eight hundred sixty-seven (867) cases were analyzed (Table V).

TABLE V

CONDITIONS UNDER WHICH DEATH OCCURRED WITH CORONARY SCLEROSIS (867 CASES)

CONDITION	WITH HYPERTENSION			WITHOUT HYPERTENSION			TOTAL	
Effort	21		2.5%	67		7.5%	88	10%
work		43%			77.5%			69.5
play		9.5			6.0			7.0
other effort		47.5			16.5			23.5
Rest	328		38%	324		37%	652	75%
hospital		78%			52.5%			65
bed		9			14.0			11.5
room		2			7.0			4.5
home		9			14.0			11.5
other rest		2.5			12.5			7.0
Miscellaneous	34		4%	93		10.5%	127	14.5%
bathroom		20.5%			15%			16.5
found dead or sudden		76.5			79.5			78.5
eating		3.0			1.0			1.5
excitement		0			4.5			3.0
Total	383		44.5%	484		55.5%	867	100%
Total noneffort	362		41.5%	417		48%	779	90%

Ten per cent died while engaged in some effort, as work, play, going through a fire test, policeman arresting a man, running up a flight of stairs, changing a tire, running to catch a streetcar, wrestling, packing a suitcase, sneezing, etc. A greater per cent in the nonhypertensive group died while at work, probably because they were able to work. In other forms of effort the greater percentages were in the hypertensive group.

In 75 per cent of the 867 cases analyzed death occurred while the patient was at rest, as in the hospital, in bed, in a room, at home, in a chair, in a sleeping car, in a saloon, in jail, in a doctor's office, picking flowers, in a barber's chair, in an elevator, in a streetcar, in a taxicab, in an automobile, and on a train. The numbers were about equal in the hypertensive and nonhypertensive groups. The greatest number were at rest in the hospital. The final condition which sent the patients to the hospital, except in a very few cases, was not in any way associated with effort. Most of the patients came to the hospital on account of symptoms of congestive heart failure. Some came because of noncardiac conditions, as hypertrophy of the prostate, etc.

Fourteen and one-half per cent of the 867 cases were placed in the miscellaneous group, because the conditions under which these patients died could not be related to effort or rest. There seemed to be a definite relation between going to or coming from the bathroom and coronary attacks. Sixteen and one-half per cent of those in this miscellaneous group died at such a time. Those found dead or those who died suddenly comprised 78.5 per cent of the group. Only a small number died while eating. Excitement seemed to have little to do in precipitating an attack.

It is of interest to note the small number (10 per cent) who died while at work or while engaged in any effort and the larger number (75 per cent) who died while at rest. These facts might have some bearing upon the pathologic physiology concerned in bringing about death in coronary sclerosis. Blood pressure is lower at rest. This might aid in the formation of a thrombus. There appears to be no indication of a tendency for death from coronary occlusion to occur while at work. The contrary is suggested.

The great contrast in the number of those who died while at rest and those who were working (652:88 or 7.4:1) is significant from the standpoint of workmen's compensation. The number dying with effort is probably not more than would be expected under the natural course of events.

PATHOLOGY

The anatomic changes noted in cases of death from coronary disease are for the most part seen best by gross examination, but the minute changes in the vessels and most of the fibrosis of the myocardium require the aid of a microscope. The things observed are atherosclerosis and thrombosis in the vessels, and hypertrophy, fibrosis, infarction, and rupture of the myocardium. Mural thrombosis following infarction is seen on the endocardium. Noninfectious pericardial adhesions, fibrinous and fibrous, are seen over the infarcted areas. There are also the associated pathologic changes, as passive congestion and edema.

Vessels.—The degree of involvement in the left and right coronary arteries is shown in Table VI. The degree of sclerosis is expressed in

grades of + to ++++. Four plus indicates severe thickening and calcification of the coronary arteries, so that the lumens are completely closed as far as can be determined by gross examination. The degree indicated by + is but a slight amount of intimal thickening; ++ and +++ are intermediate stages.

TABLE VI

DEGREE OF SCLEROSIS IN THE CORONARY ARTERIES IN CASES IN WHICH DEATH WAS DUE TO CORONARY SCLEROSIS (900 CASES)

DEGREE OF LEFT AND RIGHT CORONARY SCLEROSIS	WITH HYPERTENSION		WITHOUT HYPERTENSION		TOTAL	
Both +++ to ++++	244	59.5%	279	57%	523	58%
Left ++++ Right ++	65	15.5	85	17	150	17.5
Left ++++ Right +	41	10.0	80	16	121	13.0
Left +++ Right ++	20	5.0	18	3.5	38	4.0
Left +++ Right +	17	4.0	15	3.0	32	3.5
Left ++ Right ++	15	3.5	6	1.0	21	2.5
Left ++ Right +	1	0.2	4	1.0	5	0.5
Right ++++ Left ++	5	1.0	1	0.2	6	0.5
Right ++++ Left +	2	0.5	2	0.5	4	0.5
Right +++ Left ++	0	0.0	0	0.0	0	0.0
Right +++ Left +	0	0.0	0	0.0	0	0.0
Right ++ Left +	0	0.0	0	0.0	0	0.0
Total	410	99.2	490	99.2	900	100.0

In 900 cases the description of coronary involvement was complete enough to permit a fairly accurate evaluation of the degree of sclerosis. Fifty-eight per cent showed involvement of +++ to ++++ in both arteries. In 17 per cent there was involvement of +++ in the left coronary and ++ in the right. In 13 per cent it was left ++++ and right +. Involvement of left +++ and right ++ comprised 4 per cent. Left +++ and right + comprised 3.5 per cent. Two and one-half per cent of the patients died with what was estimated as left ++ and right +. Right ++++ and left ++ and right ++++ and left + were small, 0.5 per cent each.

The left coronary artery, generally the anterior descending branch, was the one most severely affected. It was also found that fewer deaths resulted from right arterial involvement than from left, with the same degree of involvement. The percentage of deaths in the hypertensive and nonhypertensive groups with a like amount of arterial change was practically the same.

Thrombosis of one or both coronary arteries is a common complication of coronary sclerosis. Thrombosis of a nonsclerotic vessel is rare. Coronary emboli, except for small emboli in subacute bacterial endocarditis, are also rarely seen. When they do occur there is no relation to coronary sclerosis.

Nine hundred nineteen of our cases were sufficiently well described to determine that coronary thrombosis was present. Thrombosis of one or both coronary arteries was found in 45.5 per cent of the cases (Table VII). It was present in the left artery in 32.5 per cent, in the right in 10 per cent, and in both in 3 per cent of the cases.

TABLE VII

FREQUENCY OF THROMBOSIS WITH CORONARY SCLEROSIS (919 CASES)

ARTERIES	WITH HYPERTENSION (410)		WITHOUT HYPERTENSION (509)		TOTAL	
Left	158	38.5%	143	28%	301	32.5%
Right	48	11.5	43	8.5	91	10
Both	14	3.5	13	2.5	27	3
Total	220	53.5	199	39.0	419	45.5

Thrombosis was more common in the hypertensive group (53.5 per cent) than in the nonhypertensive group (39 per cent). There was gross evidence of thrombosis in less than half of the deaths from coronary disease. Its occurrence was less in the group without hypertension, in which sudden death was more common.

Myocardium.—The pathologic conditions observed in the myocardium were hypertrophy, infarcts, mural thrombi, and areas of fibrosis not due to infarcts. The latter may require microscopic examination for their detection, but gross, irregular areas of fibrosis are not infrequently seen.

Cardiac enlargement was the most common change observed in the myocardium. In speaking of cardiac enlargement it is necessary to know whether enlargement as shown roentgenologically is meant, or hypertrophy which is indicated by increase in size and weight at autopsy. Increase in size as shown roentgenologically indicates dilation, while increase in weight represents hypertrophy. The two conditions, however, are regularly associated. The enlargement mentioned in this paper is that observed at autopsy and is due to hypertrophy (increase in weight).

TABLE VIII

CARDIAC ENLARGEMENT (HYPERTROPHY) IN CASES OF CORONARY SCLEROSIS (923 CASES)

GRAMS	WITH HYPERTENSION (414)		WITHOUT HYPERTENSION (509)	
	MALES	FEMALES	MALES	FEMALES
250-299	0	3	23	5
300-349	6	10	82	24
350-399	9	15	151	22
400-499	16	14	125	20
450-499*	19	46	57	
500 or more	276			
Total	326	88	438	71
	3.6%	3.1%	50.3%	5.7%

*450, or more, for females.

Cardiac hypertrophy, as indicated by a weight of 400 gm., or more, in males, and 350 gm., or more, in females, was noted in all but twenty-eight of the 414 cases (93.2 per cent) in the hypertensive group (Table VIII). An increase in heart weight was not so common in the nonhypertensive group; 224 of the 509 (44 per cent) showed hypertrophy. In the total of 923 cases hypertrophy was noted in 610 (66 per cent); 34 per cent of the entire group showed no hypertrophy. All had severe coronary sclerosis. A causal relationship between coronary sclerosis and hyper-

trophy is not supported. It seems more reasonable to believe that the hypertrophy was due to hypertension, which was noted with practically the same frequency as the hypertrophy.

Two theories have been advanced to support the belief that cardiac hypertrophy may be due to coronary sclerosis: (1) compensatory hypertrophy of heart muscle following myocardial fibrosis, and (2) hypertrophy due to ischemia of the heart muscle.

TABLE IX

DEGREE OF MYOCARDIAL FIBROSIS ASSOCIATED WITH CORONARY SCLEROSIS (37 CASES)

	CORONARY SCLEROSIS		MYOCARDIAL FIBROSIS	
Severe	37	100%	18	48.5%
Slight	–	–	17	46
Absent	–	–	2	5.5

The compensatory hypertrophy theory, while seeming to have some reasonable basis, is not borne out by microscopic findings in the myocardium in cases of coronary sclerosis (Table IX). Thirty-seven hearts were examined. Severe coronary sclerosis was present in all and there was also cardiac hypertrophy in all, but myocardial fibrosis of a severe degree was present in only 48.5 per cent of the cases. Such fibrosis is just as common in hearts which are the seat of coronary sclerosis but are not hypertrophied.

TABLE X

DEGREE OF CARDIAC HYPERTROPHY IN SYPHILITIC HEARTS IN CASES IN WHICH DEATH WAS DUE TO NARROWING OF THE CORONARY ORIFICES

	SEX	MARGINAL THICKENING OF CUSPS	SEPARATION OF COMMISSURES	WEIGHT OF HEART (GM.)
1	F	–	–	275
2	F	–	–	280
3	M	–	–	305
4	F	+	+	315
5	M	+	+	350
6	M	+	+	360
7	M	–	–	360
8	F	–	–	375
9	F	–	–	385
10	M	–	–	395
11	M	–	–	395
12	M	–	–	400
13	M	–	–	415
14	M	–	–	435
15	M	+	+	600

If cardiac ischemia can cause hypertrophy it should be present in cases of syphilitic aortitis with narrowing of the coronary orifices without syphilitic valvulitis. Table X shows fifteen cases in which death was due to syphilitic narrowing of the coronary orifices. Hypertrophy to any marked extent was present in only one, and in this case the hypertrophy could be accounted for by aortic insufficiency resulting from separation

of the commissures or from free marginal thickening of the aortic cusps. Both conditions were present in this case.

Autopsy findings, gross or microscopic, offer little or no support to the theory that cardiac hypertrophy is a result of coronary sclerosis. The hypertrophy which is commonly associated with coronary sclerosis is most likely due to a coexisting primary hypertension which, as shown above, is probably present in 69 per cent of the cases of coronary sclerosis.

Infarction of the myocardium was seen in 30.5 per cent of 919 of our cases (Table XI). This was less common than thrombosis. Some patients with coronary thrombosis do not live long enough to develop gross anatomic evidence of infarction. The infarction occurred with thrombosis in 23.5 per cent of the cases and without thrombosis in 7 per cent. It is highly possible that some of the thrombi may have been missed by the pathologists, but infarcts do occur at times without a coronary thrombus. This is seen occasionally in cases with syphilitic aortitis with narrowing of the coronary orifices. As was seen with coronary thrombosis, infarction was nearly twice as common in the hypertensive group (40 per cent) as in the nonhypertensive group (22 per cent).

TABLE XI

	WITH HYPERTENSION		WITHOUT HYPERTENSION		TOTAL	
Frequency of Infarction With Coronary Sclerosis (919 Cases)						
With thrombus	135	32%	82	16%	217	23.5%
Without thrombus	34	8	30	6	64	7
	169	40	112	22	281	30.5
Frequency of Rupture of the Heart With Coronary Sclerosis (919 Cases)						
	20	5%	25	5%	46	5%

Rupture of the myocardium, with hemopericardium, was observed in 5 per cent of 919 cases examined (Table XI). It was usually associated with a thrombus. Sometimes there was rupture of a coronary branch, but generally the rupture was due to a softened infarct.

With myocardial infarction, if the patient lived for a few hours, or more, a mural thrombus developed, generally in the wall of the left ventricle, but sometimes in the right ventricular wall, or both. Embolic phenomena were common. Paralysis or symptoms of infarction of the lung were common early complaints of the patients.

Gross or microscopic areas of fibrosis are not infrequently seen in the myocardium in cases of death from coronary disease. This fibrosis is irregular in distribution. It appears to be due to a slow replacement of muscular tissue by connective tissue. The areas of fibrosis are not located immediately around blood vessels, as are the scars due to rheumatic inflammation. The myocardium was carefully studied microscopically in thirty-seven cases in which death was caused by coronary disease. In no case was there an infarct. Severe coronary sclerosis was present in all (Table IX). Severe myocardial fibrosis was seen in 48.5 per cent, slight

fibrosis in 46 per cent, and none in 5.5 per cent. The impression was gained that, except for rupture of the myocardium and some large infarcts, the anatomic changes observed in the myocardium in cases of coronary sclerosis are not sufficient to be the cause of death. The pathologist has not been able to find the final cause of death.

Pericardium.—Infectious pericarditis was not found in any of our cases. A fibrinous exudate regularly developed on the epicardium over recent infarcts. If the patient lived, these fibrinous exudates organized and resulted in a localized area of fibrous adhesions between the two layers of the pericardium.

Other Pathologic Findings.—The chief associated pathologic conditions observed were evidences of congestive cardiac failure, which was indicated by edema or chronic passive congestion of the liver.

The presence of edema was determined by the occurrence of anasarca, hydrothorax, or ascites (Table XII). Sufficient histories or pathologic descriptions were given in 919 cases to determine the presence or absence of edema. In the 410 patients with hypertension, edema was noted in 52 per cent. Edema was seen in only 21.5 per cent of the 509 patients without hypertension. In the total of 919, edema was observed in 35 per cent. It was more than twice as common in the hypertensive group.

TABLE XII

FREQUENCY OF EDEMA (ANASARCA, HYDROTHORAX, ASCITES) WITH CORONARY SCLEROSIS (919 CASES)

EDEMA	WITH HYPERTENSION		WITHOUT HYPERTENSION		TOTAL	
Present	213	52%	110	21.5%	323	35%
Absent	197	48	399	78.5	596	65
Total	410	100	509	100	919	100

Nine hundred nine (909) cases could be evaluated in respect to the existence of chronic passive congestion of the liver (Table XIII). Chronic passive congestion was evident in 55 per cent of the hypertensive group and in 23 per cent of the nonhypertensive group. Of the entire group of 909 cases, chronic passive congestion of the liver was present in 37.5 per cent. As with edema, chronic passive congestion of the liver was more than twice as frequent in the hypertensive group as in the nonhypertensive group.

TABLE XIII

FREQUENCY OF CHRONIC PASSIVE CONGESTION OF THE LIVER WITH CORONARY SCLEROSIS (909 CASES)

PASSIVE CONGESTION	WITH HYPERTENSION		WITHOUT HYPERTENSION		TOTAL	
Present	225	55%	116	23%	341	37.5%
Absent	185	45	383	77	568	62.5
Total	410	100	499	100	909	100

SUMMARY

Nine hundred twenty-eight (928) cases of coronary sclerosis were studied. Deaths resulting from coronary sclerosis represented about one-fourth of all deaths from noncongenital cardiac disease, or about 4 per cent of all deaths in patients above 6 months of age, in the autopsy material in the Department of Pathology at the University of Minnesota from 1910 to 1936, inclusive.

Nothing definite can be said concerning the primary cause of the disease. Death occurred most frequently in the fifth, sixth, seventh, and eighth decades, but it may take place early in the third decade. Death from coronary sclerosis was about two and one-half times as common in males as in females. Hypertension was the most common condition associated with coronary sclerosis. The great frequency suggested a causal relation.

Sudden death or death following symptoms of but a few minutes' duration was common (28 per cent). Such deaths were more common in the patients without hypertension than in those with hypertension. In patients with symptoms lasting one to five years, or more, hypertension was more common.

Pain was the most common complaint, being present in more than half of the cases. The location and variety of the pain had a marked variation. Dyspnea was the next most common symptom. Fainting, dizziness, and paralysis were not uncommon.

Effort was not a conspicuous factor in the death of these patients (10 per cent). At least 75 per cent died while at rest in the hospital or elsewhere.

The left coronary artery, especially the anterior descending branch, was the one most frequently involved. Severe right coronary involvement without a relatively severe affection of the left coronary artery rarely caused death.

Thrombosis of the arteries was present in nearly half the cases (45 per cent), 32.5 per cent in the left alone, 10 per cent in the right alone, and 3 per cent in both arteries. Thrombosis was more common in the patients with hypertension than in those without hypertension.

Hypertrophy was more than twice as common in the hypertensive as in the nonhypertensive group. There was no evidence to support the claim that cardiac hypertrophy results from coronary sclerosis. On the other hand, the hypertrophy appeared to be the result of essential hypertension.

Infarction of the myocardium was noted in 30.5 per cent of the entire group but was more frequent among the cases of hypertension. In most cases the infarction was preceded by thrombosis. Rupture of the myocardium was relatively rare (5 per cent). Some myocardial fibrosis was observed in nearly all of the hearts examined, severe in 48.5 per cent, slight in 46 per cent, and absent in 5.5 per cent.

Pericardial fibrous adhesions were noted, as a rule, only about infarcted areas.

Edema and chronic passive congestion of the liver were frequently present, but more commonly in the hypertensive group.

Excepting thrombosis, infarction, and rupture of the myocardium, the anatomic changes noted did not appear to be sufficient to be the final cause of death. In more than half of the cases, something not manifested anatomically had to be assumed to be the cause of death.

CONCLUSIONS

1. Coronary sclerosis of the atherosclerotic type, with or without thrombosis and infarction, is the most common cause of cardiac sudden death.

2. Pain is the most frequent symptom.

3. Most patients die while at rest, and only a relatively small number during effort.

4. Hypertension is the outstanding suggested etiologic factor.

5. Males predominate over females in the ratio of 2.5 to 1.

6. The disease is primarily one of adults but may be seen in younger people.

7. The incidence and degree of sclerosis are much greater in the left coronary artery than in the right.

8. Besides sclerosis of the arteries (100 per cent), the chief anatomic changes noted are thrombosis (45 per cent), hypertrophy (66 per cent), infarction (30.5 per cent), rupture of myocardium (5 per cent), and myocardial fibrosis (severe, 48.5 per cent; slight, 46 per cent; and none, 5.5 per cent).

9. Edema was noted in 35 per cent of the cases, more frequently in the hypertensive group. Chronic passive congestion of the liver was seen with about the same frequency in the two groups.

10. In more than half the cases an anatomic change considered sufficient to cause death was not evident.

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BLOOD OXYGEN CHANGES FOLLOWING INTERMITTENT VENOUS OCCLUSION*

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THE most important investigation of reactive hyperemia which has been made to date is the study published by Lewis and Grant[1] in 1925, more than fifty years after Cohnheim first described the phenomenon and more than twenty-five years after Bier applied its present name to it and suggested a possible therapeutic application for it. The conclusions of Lewis and Grant, which were arrived at by direct visual observation and by volumetric studies with the plethysmograph, are substantially as follows:

1. Occlusion followed by release of the arterial supply of an extremity brings about a degree of vasodilatation which is proportionate to the duration of the occlusion, within certain limits; generally speaking, an occlusion of five seconds is necessary to produce any perceptible reaction, and the reaction lasts a half to three-quarters as long as does the previous period of circulatory arrest. The reaction is greater in a limb the temperature of which is raised, though it is unaffected by changes of external temperature.

2. The reaction affects not only the superficial vessels, as evidenced by changes in the color of the skin, but also the deeper vessels, as proved by volumetric studies and by measurement of the inflow to the limb.

3. A similar reaction occurs when venous pressure is increased. Both the degree and the duration of the reactive hyperemia increase as the congestion is raised from 40 mm. Hg, the minimum necessary to produce any perceptible reaction, and at very high venous pressures the reaction is very like that produced by arterial occlusion. Within certain time limits both the degree and the duration of the reaction are increased by the duration of the congestion.

4. The reaction is a local one and is independent of both the central nervous system and the local reflexes.

Bier's suggestion that active or passive venous congestion be employed in the treatment of pathologic states of the soft tissues has been accepted for many years, though the mechanism of its favorable action has never been satisfactorily explained. Formerly this method of treatment was applied only to diseases in which the arterial blood supply was not primarily involved, but recently, and still more or less empirically, it has been applied to conditions in which an arterial deficiency is the basic pathologic change.

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Collens and Wilensky[2] have recently applied the principle of reactive hyperemia in the treatment of peripheral vascular diseases, and have also described a simple apparatus for producing the hyperemia. In 1937, de Takáts, Hick, and Coulter[3] reviewed the whole subject of reactive hyperemia and reported the use of the Collens and Wilensky technique in ten patients. In their cases, however, statements concerning its good results must be somewhat qualified, for other methods of treatment were also employed, and other factors thus introduced. It is worth mentioning that these authors issue a specific warning that the same contraindications should be observed in the use of reactive hyperemia in the treatment of peripheral vascular disease as are observed in the use of alternate suction and pressure therapy.

The underlying mechanism of the phenomenon needs much further investigation. In true reactive hyperemia there is a marked increase in the blood volume flow, as is proved by the objective color changes in the skin, which are in turn evidence of an increased amount of arterial blood in the venous system. If intermittent venous occlusion produces a true reactive hyperemia, it also should be associated with an increase in the blood volume flow, which in turn should be evidenced by a rise in the oxygen content of the venous blood. The studies of de Takáts and his associates would seem to prove the contrary. Their observations on the percentage of oxygen saturation of the blood at intervals of twenty and forty minutes after the release of intermittent venous compression fail to show any increase, but, on the contrary, show an actual decrease.

The explanation of the findings of de Takáts, et al., is not far to seek. The duration of reactive hyperemia produced by complete occlusion of the vascular system of an extremity is transitory, and it seems scarcely reasonable to expect to demonstrate blood changes much beyond the period of its existence. This present communication is a report of a study of the oxygen saturation of the blood made during the period in which the reactive hyperemia should be demonstrable.

TECHNIQUE OF EXPERIMENTS

The investigation was conducted upon eleven healthy male subjects, with normal cardiovascular systems, and the circumstances of the test were identical in each instance. Each test was preceded by a rest period of thirty to sixty minutes, during which the patient lay on a table, at room temperature, with his arms stretched beside his body at heart level. A blood pressure cuff was so adjusted on the arm to be studied that it could be instantly released. All samples of blood were collected under oil from the antecubital vein, without the use of a tourniquet, the needle being left in situ whenever successive specimens were collected. The Van Slyke[4] method for determination of the oxygen content of the blood was used throughout.

After a control sample of blood had been collected at the conclusion of the rest period, the first test was undertaken, as follows: The arm was elevated to empty the veins, the blood pressure cuff was abruptly inflated to 250 mm. Hg, and the arm was returned to heart level. Then, at periods varying from five to eight minutes in

each subject, the cuff was deflated equally suddenly and the return of circulation permitted. Samples of blood were collected one minute and three minutes after the release of the occlusion.

In the second test the blood pressure cuff was inflated with the arm at heart level, and intermittent venous occlusion was instituted over periods ranging from fifteen to sixty minutes. In all cases the duration of the compression was a period of two minutes, but the interval of release was variously one minute and two minutes. The range of pressure was from 60 to 80 mm. Hg. Specimens of blood were withdrawn, as in the first test, one minute and three minutes after the final release of the occlusion.

RESULTS

The percentage of the oxygen saturation of the blood after complete vascular compression and after intermittent venous occlusion, as compared with the percentages in the resting period, are shown in Tables I and II, the findings of which may be briefly summarized.

TABLE I

OXYGEN CHANGES IN VENOUS BLOOD AFTER RELEASE FROM COMPLETE VASCULAR OCCLUSION

CASE NUMBER	PERCENTAGE OF OXYGEN SATURATION RESTING STATE	PERCENTAGE OF OXYGEN SATURATION 1 MIN. AFTER RELEASE	PERCENTAGE OF OXYGEN SATURATION 3 MIN. AFTER RELEASE
1.	62	77	91
2.	86	70	86
3.	61	77	
4.	63	69	58
5.	66	88	93
6.	78	97	84
7.	53	90	85
8.	81	95	81
9.	75	75	66
10.	60	90	89
11.	85	96	94

After complete arterial occlusion for five to eight minutes (Table I) there was a definite rise in the oxygen saturation of the blood from the antecubital vein in nine of the eleven cases studied at the end of one minute after the pressure was released; in one case the percentage was unaltered, and in another there was a fall of sixteen points. At the end of three minutes the oxygen-saturation percentage was still increased over the resting period in six of ten cases; in two cases the percentage was unchanged, and in two there was a slight fall. In some individuals the return to normal levels was rapid, in others the elevation tended to persist, but the general tendency of the whole group was toward an increase in the oxygen saturation of the blood.

After intermittent venous occlusion, however, the tendency was exactly reversed. In eight of the eleven cases (Table II) there was a definite decrease in the oxygen saturation of the blood at the end of one minute after the release of the compression, and an increase in only three cases.

The tendency was less clearly defined at the end of three minutes; in eight cases studied at that time there was a decrease of the oxygen saturation in four, a very definite elevation in two, and in two others an elevation of one and three points, respectively, which can probably be disregarded, as a 5 per cent variation must be allowed as within the range of normal laboratory error.

TABLE II

OXYGEN CHANGES IN VENOUS BLOOD AFTER INTERMITTENT VENOUS OCCLUSION

PERIOD OF TEST	CASE NUMBER	PERCENTAGE OF OXYGEN SATURATION RESTING STATE	PERCENTAGE OXYGEN SATURATION 1 MIN. AFTER RELEASE	PERCENTAGE OF OXYGEN SATURATION 3 MIN. AFTER RELEASE
15 minutes	1.	62	55	
18 minutes	2.	61	46	50
30 minutes	3.	80	75	75
30 minutes	4.	73	50	58
30 minutes	5.	66	55	85
45 minutes	6.	78	68	81
45 minutes	7.	56	68	
45 minutes	8.	85	81	
1 hour	9.	75	69	67
1 hour	10.	60	61	62
1 hour	11.	82	92	88

SUMMARY

The results of this study would seem to indicate that complete vascular occlusion in the presence of a normal circulatory system is followed by a true reactive hyperemia immediately upon release of the compression. The maintenance of complete compression over periods of five to eight minutes was generally followed by a definite rise in the oxygen saturation of the venous blood one minute after its release, and in most cases the elevation was maintained at the end of three minutes. It may therefore be assumed that the reactive hyperemia produced by this type of occlusion brings about a more rapid flow of blood through the extremity, as well as a marked increase in the volume of the flow.

Intermittent venous occlusion, on the other hand, even in the presence of a normal circulatory system, is usually followed by a lowering of the oxygen saturation of the venous blood at one minute as well as three minutes after the release of the occlusion. This would seem to indicate that under the circumstances of this test (with a pressure varying from 60 to 80 mm. Hg, and with a ratio of compression and release of 2:2 and 2:1) a true reactive hyperemia is not produced. Any favorable effects claimed for this type of therapy must therefore result not so much from an increase in the rate or the volume of the blood flow as from some chemical changes produced in the tissues incident to the venous congestion and the changes produced by the increased venous pressure.

It might be said in conclusion that these findings bear out those of Allen and McKechnie[5] in their study of the effect of intermittent venous occlusion on the skin temperature under controlled circumstances. In nineteen patients (nine normal subjects, and ten with hypertension, arthritis, and peripheral vascular disease) they found no evidence that any significant or consistent vasodilatation resulted from the procedure.

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THE NORMAL HEART VOLUME IN MAN

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WHEN trying to determine the size of the heart in the living subject reliance has usually been placed mainly on the values established from measurements on the frontal orthodiagrams alone. Though the results thus obtained have sometimes been of importance—e.g., for comparative studies of the heart on different occasions—the practical use of the method has been greatly hampered by the fact that the heart volume cannot be determined in this way with a sufficient degree of accuracy. The main objection is, of course, that frontal orthodiagrams alone can be employed for this purpose only if the form of the heart is the same not only in one individual under different conditions, but also in different individuals. As is well known, this is far from being the case (see below), great variations often occurring in the form of the heart. Under these circumstances it has been found necessary to try to arrive at more exact methods for establishing the heart volume. Thus Palmieri[1] (1920), Lysholm[2] (1926), and Wegelius[3] (1934) made models of the heart with the aid of projections in several planes. This modeling procedure, however, takes a long time and will therefore hardly be of practical importance. It was a great advance in this field when it was shown independently by Rohrer[4] (1916-1917) and Kahlstorf[5] (1932) that it is possible to calculate the volume of the heart with satisfactory accuracy from the frontal and sagittal orthodiagrams. They assumed that the heart is of a shape between a paraboloid and an ellipsoid. The size of the heart can then be calculated according to the formula $V = 0.63 \cdot F_a \cdot L_{max}$, where V is the volume of the heart, F_a the area of sagittal orthodiagram, and L_{max} the maximum depth of the transversal orthodiagram. The reliability of this calculation was demonstrated by Kahlstorf, who investigated nine normal and three pathologic hearts from corpses. The hearts had been hardened in formalin and were mounted on a stand; orthodiagrams were made in two directions at right angles. Each preparation was investigated in three different positions, and the values obtained were compared with the volume as found by water displacement. The agreement was very good, the difference between the calculated and observed volumes being not more than ± 5 per cent. The method was applied to determinations of the normal heart volume in living persons by Rohrer in seven cases. In five of these the values lay between 471 and 575 c.c.; in one, obviously a very small individual (height 140 cm.), it was only

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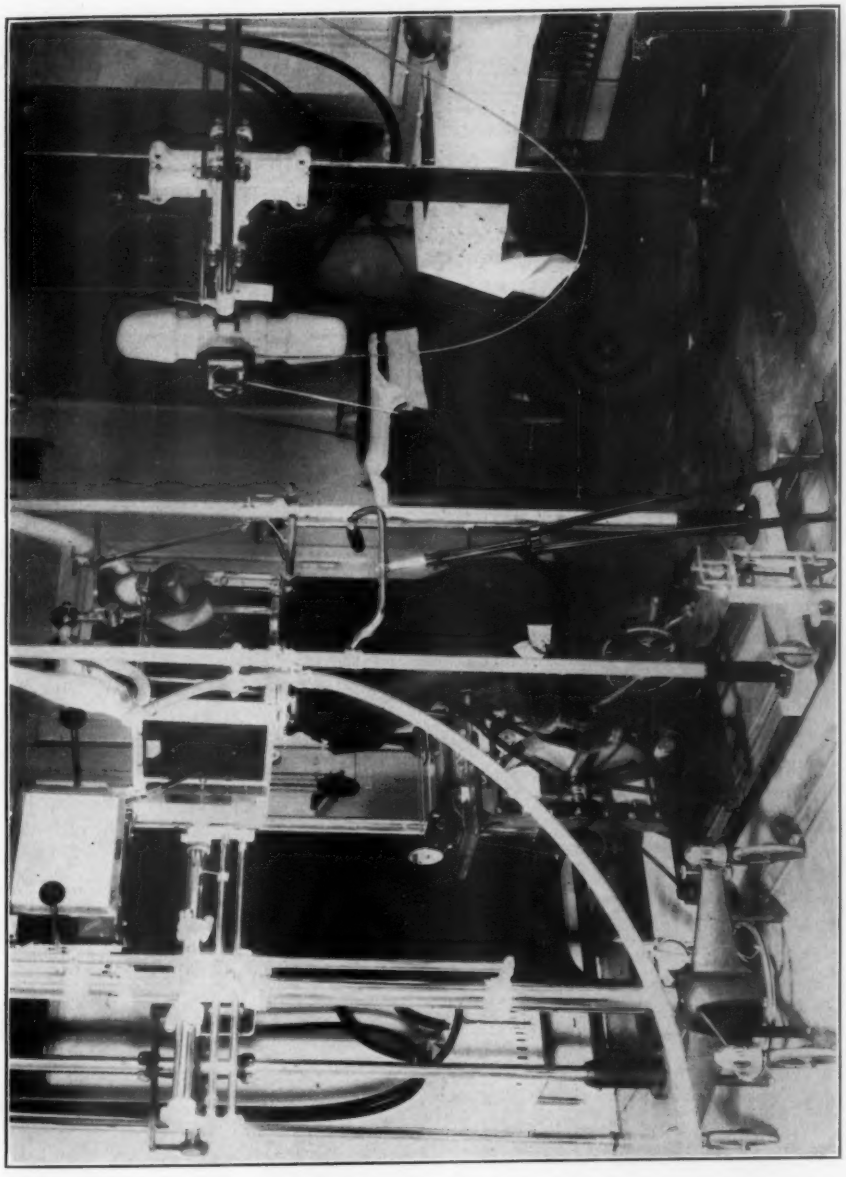

Fig. 1.—General arrangement of the apparatus for the determinations.

216 c.c.; and in the remaining subject (height 170 cm.) 762 c.c. Kahlstorf has examined a much larger group, comprising seventy men and fifty women. All of his determinations were made with the subject in the standing position, a fact of some importance, since it is known that the heart is considerably larger when the subjects are in the recumbent than when they are in the erect position (cf. Nylin,[6] 1934). Kahlstorf calculates his values in relation to the body weight (he finds a direct proportion between them) and arrives at the conclusion that the heart volume per kg. of body weight is at least 7 c.c. in female and 8 c.c. in male subjects, and that it does not exceed 11 c.c. For the erect position Lysholm, Nylin, and Quarnå[7] (1934) have determined the heart volume in thirty-three normal male subjects according to the Rohrer-Kahlstorf formula. The average was 627 ± 22 c.c., the extreme limits observed being 393 and 860 c.c.. As far as can be judged, their values agree well with those of Kahlstorf.

The following investigation on the normal heart volume was carried out on a larger number of subjects; they were young students, 20 to 30 years of age, and bank clerks between the ages of 37 and 47 years, all of whom were in perfect health and exhibited no signs of heart or vascular disease.

For our determinations the devices for biplane radiography were constructed around a Krogh ergometer bicycle and manufactured in the shops of Mr. G. Schönander in 1935 (Fig. 1). In front of and at the side of the subject were placed two films at right angles. Corresponding to these were two 40 kw. roentgen tubes with rotating anodes, mounted on special stands and placed at a distance of 1.5 and 2 M. from the films. The high tension was adjusted to 90 kv. peak, the tubes being coupled in parallel. The milliamperage was so regulated that the tube corresponding to the side view had a load of 250 Ma., and the other tube 200 Ma. The high tension switches (*s* in Fig. 2) enabled us to use each tube separately or both simultaneously. The arrangement was constructed in the autumn of 1935 by the firm of Siemens Reiniger Veifa, in Stockholm, and has since worked satisfactorily. During the exposure, the front and the side of the chest were gently pressed against the two cassette-holders. The exposure time was one-twentieth second. To cut off scattered radiation during simultaneous exposures, two crossed Lysholm all-metal grids were used in each of the two planes. This arrangement satisfactorily eliminates the scattered radiation and prevents blurring in the roentgenogram.

For the calculation of the heart volume, it is necessary to introduce a correction for the enlargement of the heart shadow on the film. Fig. 3 illustrates this. Assuming the heart to be an ellipsoid, one gets the volume V from the equation: $V = \frac{4\pi}{3} \cdot \frac{200-a}{200} \cdot \frac{l}{2} \cdot \frac{200-a}{200} \cdot \frac{m}{2} \cdot \frac{150-b}{150} \cdot \frac{n}{2}$, where l and m are the axes of the ellipsoid on the frontal and n the axis on the lateral view, and a and b the distances from the center of the heart to the films. Direct measurements gave for a and b, 15 and 23 cm., respectively, so that the formula is reduced to $V = 0.38 \cdot l \cdot m \cdot n$.

We have thus assumed the heart to have the form of an ellipsoid, whereas the Rohrer-Kahlstorf formula takes it to be something between

a paraboloid and an ellipsoid. Thus they get the constant 0.63, whereas here it is 0.67. Our values will therefore be 6 per cent higher than those of Rohrer and Kahlstorf.

In order to determine the margin of error for the method, we have made double exposures on ten healthy medical students. The values obtained are given in Table I. We find the margin of error as small as 30 c.c., corresponding to 4.7 per cent of the mean value.

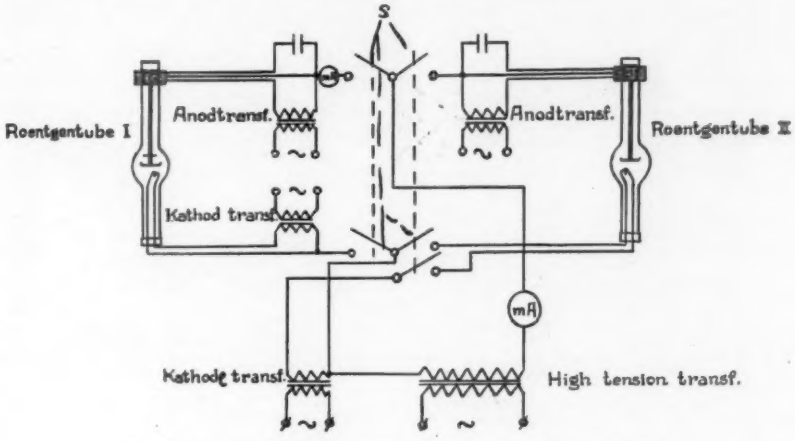

Fig. 2.—Arrangement of roentgen tubes (*s*, switches).

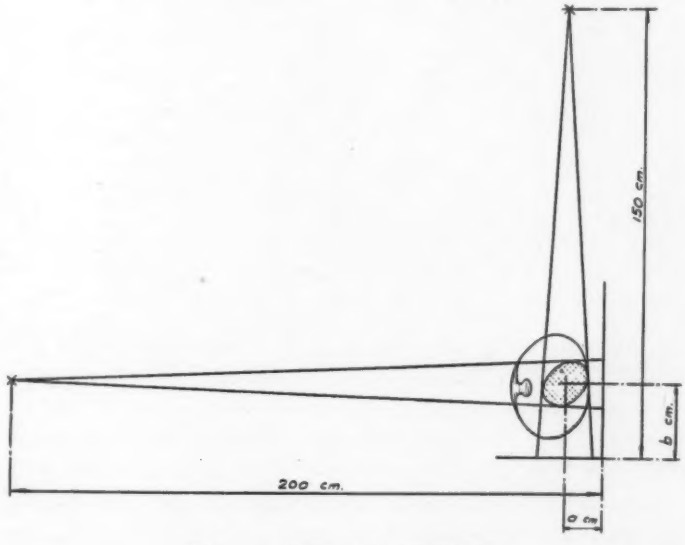

Fig. 3.—Scheme for correction.

Before giving the details of our observations we should like to exemplify by means of two cases the paramount importance of taking into consideration two projections in different planes for the estimation of the heart volume. Fig. 4 shows the frontal and sagittal teleroentgeno-

grams of a healthy nurse in a sitting position. On the frontal projection the heart looks enlarged, but the sagittal diameter is exceedingly short. The subject had a very flat chest. Calculating the heart volume according to the Rohrer-Kahlstorf formula, we get the normal value of 900 c.c., or 450 c.c./m² of body surface. On the other hand, if the heart volume is calculated only on the basis of the frontal roentgenogram with the help of Bardeen's[8] formula (1918), it amounts to 1,300 c.c., which is 45 per cent higher than the value obtained by the method first mentioned. Fig. 5 illustrates the reverse situation in another normal subject, also in a sitting position. Here the heart is tubular, as shown by the frontal roentgenogram, but the chest is deep, and the sagittal diameter fairly large. The heart volume according to Bardeen's formula is 400 c.c., but by the Rohrer-Kahlstorf method we obtain 490 c.c.; thus with the former the estimate is 23 per cent too small.

TABLE I

TWO DETERMINATIONS OF HEART VOLUME ON EACH OF TEN NORMAL STUDENTS

SUBJECT	NO.	LENGTH CM.	BREADTH CM.	SAGITTAL DIAMETER CM.	HEART VOLUME C.C.	DIFFERENCE C.C.
1.	I	14	11.5	9.5	580	0
	II	14	11.5	9.5	580	
2.	I	14.5	10.5	12	690	25
	II	14.5	10.5	11.5	665	
3.	I	13	11	11	600	50
	II	12	10.5	11.5	550	
4.	I	15.5	12	10	710	50
	II	15	11.5	10	660	
5.	I	13.5	11.5	9.5	560	65
	II	13	10.5	9.5	495	
6.	I	15	12	10	690	0
	II	15	12	10	690	
7.	I	14.5	12	9.5	630	0
	II	14.5	12	9.5	630	
8.	I	15	11.5	12	790	65
	II	15	11	12	755	
9.	I	12.5	10.5	12	600	50
	II	13	11	12	650	
10.	I	14.5	12	10	660	30
	II	14.5	12	9.5	630	

General mean = 641 c.c. Mean of differences irrespective of signs = 34 c.c. Margin of the error for the method = 30 c.c. = 4.7 per cent of the mean value.

The results of our determinations on healthy men are given in Tables II and III. In the first group of seventy medical students (Table II) the absolute volume of the heart varies between 480 and 970 c.c., which is considerable. The corresponding limits are 5.6 and 14.2 c.c. per kilogram of body weight. The subject with the lower limit (No. 69) stands out as an exception, since in all the other subjects the heart exceeds 7.8 (corrected 7.4) c.c. per kilogram, which is in fairly good agreement with Kahlstorf's experiences. In seven cases, however, the values are higher than the upper limit given by Kahlstorf (11·1.06 = 11.7 c.c.). In our

smaller group of men from 32 to 47 years of age, all are at or above eight (7.5 corrected) c.c. per kilogram, but here also some subjects, in all three, have a volume larger than 11.7 c.c. per kilogram. We are thus led to the conclusion that the upper limit for the size of the normal heart is somewhat higher than given by Kahlstorf.

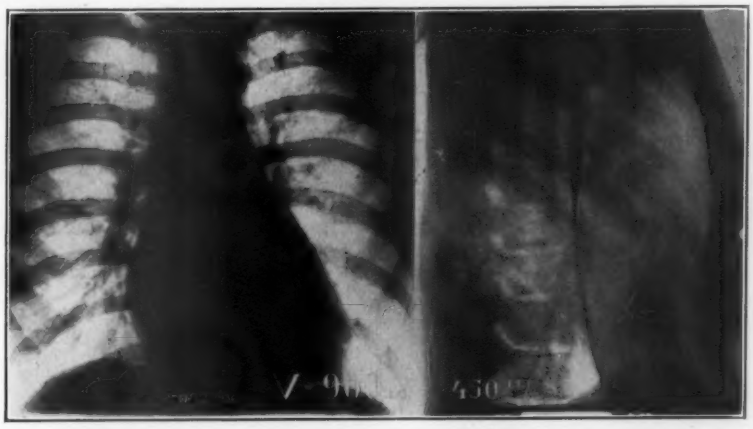

Fig. 4.—Heart volume in a healthy nurse with extremely flat chest.

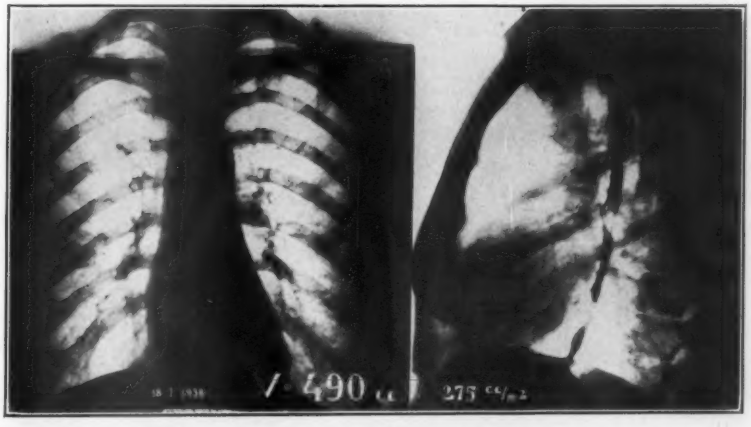

Fig. 5.—Heart volume in a healthy girl with a deep chest.

Since it has been observed in previous investigations (cf. DuBois,[9] 1936, and Grollman,[10] 1932) that metabolism and blood flow show a closer correlation to the body surface than to the body weight, it would seem natural also to correlate the heart volume with the body surface. Fig. 6 demonstrates the excellent correlation obtained in this way.

On the basis of the above-mentioned determinations, we have worked out our material statistically. The calculation of mean values and standard deviations has been made in accordance with well-known formulas.

TABLE II

HEART VOLUME OF SEVENTY HEALTHY MEDICAL STUDENTS BETWEEN 21 AND 30 YEARS OF AGE

NO.	AGE YEARS	HEIGHT CM.	WEIGHT KG.	BODY SURFACE M^2	HEART VOLUME C.C.	HEART VOLUME C.C. PER M^2	HEART VOLUME C.C. PER KG.
1.	21	175	68	1.82	530	290	7.8
2.	21	160	57	1.58	620	390	10.9
3.	22	193	91	2.22	850	380	9.3
4.	22	173	58	1.70	650	380	11.2
5.	22	177	73	1.89	850	450	11.6
6.	22	184	66	1.87	650	350	9.8
7.	22	190	86	2.14	850	400	9.9
8.	22	176	63	1.77	650	370	10.3
9.	22	176	62	1.76	680	390	11.0
10.	22	190	78	2.06	710	350	9.1
11.	22	184	81	2.04	660	320	8.1
12.	22	179	62	1.77	600	340	9.7
13.	22	172	65	1.77	830	470	12.8
14.	22	171	61	1.72	750	440	12.3
15.	22	174	64	1.77	830	470	13.0
16.	22	185	83	2.07	800	390	9.6
17.	22	168	68	1.78	660	370	9.7
18.	23	205	78	2.20	900	410	11.5
19.	23	170	66	1.77	700	400	10.6
20.	23	177	72	1.87	730	390	10.1
21.	23	184	67	1.87	550	290	8.2
22.	23	175	62	1.76	550	310	8.9
23.	23	181	76	1.96	600	310	7.9
24.	23	180	65	1.83	520	280	8.0
25.	23	176	67	1.81	750	410	11.2
26.	23	181	68	1.78	800	450	11.7
27.	23	172	66	1.78	520	290	7.9
28.	23	184	75	1.97	600	310	8.0
29.	23	176	60	1.74	480	280	8.0
30.	23	183	78	2.01	750	370	9.6
31.	23	182	69	1.68	650	390	9.4
32.	23	168	65	1.74	590	340	9.1
33.	24	180	77	1.96	850	430	11.0
34.	24	184	78	2.01	750	370	9.6
35.	24	182	71	1.92	680	350	9.6
36.	24	186	79	2.02	900	450	11.4
37.	24	180	77	1.96	830	420	10.7
38.	24	182	63	1.83	520	280	8.3
39.	24	172	69	1.81	800	440	11.6
40.	24	179	65	1.82	750	410	11.5
41.	24	169	71	1.81	750	410	10.6
42.	24	161	51	1.53	430	280	8.4
43.	24	173	65	1.78	550	310	8.5
44.	24	183	78	2.01	660	330	8.5
45.	24	181	78	1.99	650	330	8.3
46.	24	187	91	2.17	780	360	8.6
47.	24	183	78	2.01	610	300	7.8
48.	24	182	70	1.90	620	330	8.9
49.	24	170	75	1.86	580	310	7.7
50.	25	180	68	1.87	800	430	11.8
51.	25	173	76	1.91	750	390	9.9
52.	25	176	74	1.89	780	410	10.5
53.	25	175	84	1.99	970	490	11.5

TABLE II (CONT'D)

NO.	AGE YEARS	HEIGHT CM.	WEIGHT KG.	BODY SURFACE M^2	HEART VOLUME C.C.	HEART VOLUME C.C. PER M^2	HEART VOLUME C.C. PER KG.
54.	25	170	61	1.72	870	510	14.2
55.	25	189	75	2.01	600	300	8.0
56.	25	172	71	1.84	600	330	8.5
57.	25	175	69	1.84	550	300	8.0
58.	25	176	65	1.80	800	440	12.3
59.	25	176	67	1.82	690	380	10.3
60.	25	184	76	1.98	760	380	10.0
61.	26	186	75	1.98	830	420	11.1
62.	26	184	96	2.20	930	420	9.7
63.	26	175	65	1.79	580	320	9.0
64.	26	181	64	1.82	780	430	12.1
65.	26	176	68	1.84	730	400	10.7
66.	26	181	71	1.91	750	390	10.6
67.	27	179	75	1.94	780	400	10.4
68.	27	175	64	1.78	600	340	9.4
69.	29	183	85	2.07	480	230	5.6
70.	30	180	85	2.04	850	420	10.0

We have considered as normal limits the mean value decreased and increased by two standard deviations. The mean value for the heart volume for the 70 young students is found to be 700 c.c., and for the somewhat older men it amounts to 750 c.c. Calculated per kilogram of body weight (Table IV), the mean heart volume amounts to 9.8 c.c. for the younger group and 10.4 c.c. for the older one. The corresponding values per m^2 of body surface are 372 and 395 c.c., respectively. The normal limits for these 101 healthy male subjects, estimated as mentioned above, are 7.0 and 13.0 c.c. per kilogram body weight and 250 and 490 c.c. per m^2 of body surface.

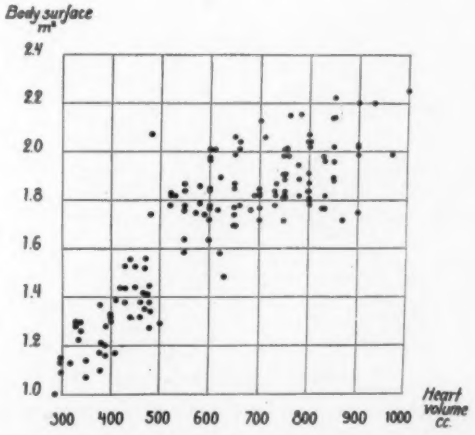

Fig. 6.—Correlation between heart volume and body surface.

TABLE III

HEART VOLUME OF THIRTY-ONE HEALTHY BANK CLERKS BETWEEN 32 AND 47 YEARS OF AGE

NO.	AGE YEARS	HEIGHT CM.	WEIGHT KG.	BODY SURFACE M^2	HEART VOLUME C.C.	HEART VOLUME C.C. PER M^2	HEART VOLUME C.C. PER KG.
1.	32	173	71	1.84	800	440	11.3
2.	32	182	83	2.02	800	400	9.6
3.	32	173	88	2.03	900	440	10.2
4.	33	171	66	1.78	730	410	11.1
5.	34	182	92	2.14	850	400	9.2
6.	34	172	61	1.72	600	350	9.8
7.	34	178	73	1.91	800	420	11.0
8.	34	172	69	1.82	730	400	10.6
9.	35	167	63	1.72	700	410	11.1
10.	35	168	75	1.85	650	350	8.7
11.	36	177	68	1.85	600	320	8.8
12.	36	190	72	1.98	750	380	10.4
13.	36	181	94	2.15	760	350	8.1
14.	37	181	67	1.88	750	400	11.2
15.	38	174	63	1.76	630	360	10.0
16.	38	187	80	2.06	650	320	8.1
17.	39	181	77	1.99	900	450	11.7
18.	39	178	84	2.02	850	420	10.1
19.	39	176	68	1.84	750	410	11.0
20.	39	183	64	1.85	700	380	10.9
21.	40	172	57	1.66	550	330	9.6
22.	40	175	72	1.87	800	430	11.1
23.	40	186	87	2.13	700	330	8.0
24.	40	178	67	1.88	850	450	12.7
25.	40	172	62	1.74	650	370	10.5
26.	42	176	60	1.75	575	330	9.6
27.	42	163	67	1.75	900	510	13.4
28.	42	188	78	2.04	800	390	10.3
29.	43	172	67	1.82	830	460	12.4
30.	44	173	68	1.83	700	380	10.3
31.	47	185	101	2.25	1000	440	9.9

TABLE IV

TOTAL HEART VOLUME, HEART VOLUME PER SQUARE METER OF BODY SURFACE AND PER KILOGRAM OF BODY WEIGHT OF 101 HEALTHY MEN

		AVERAGE M C.C.	STANDARD DEVIATION σ	V	MEAN ERROR Σ (M)	$M \mp 2\sigma$
70 medical students aged 21-30 years	Heart volume c.c.	700.7	121.9	17.4	14.6	457–945
	Heart volume c.c./m^2.	371.7	58.9	15.8	7.0	254–490
	Heart volume c.c./kg.	9.8	1.6	16.5	0.2	6.16–13.0
31 men aged 32-47 years	Heart volume c.c.	750.0	106.5	14.2	19.1	537–963
	Heart volume c.c./m^2.	394.5	45.8	11.6	8.2	303–486
	Heart volume c.c./kg.	10.4	1.3	12.4	0.2	7.8–13.6

We have not been able to establish with certainty from these investigations any pronounced difference between the age groups, even though there is a tendency toward a larger heart volume at a more advanced

age. In a previous paper, Nylin[11] (1935) calculated the heart volume of twelve healthy girls between twelve and fourteen years of age, and found that the mean value (standing) was 315 c.c. per m^2 of body surface. Comparing the results obtained for the girls and the results of this investigation (Table V), there appears to be a tendency toward an increase in the heart volume per m^2 of body surface with increasing age, but unfortunately the youngest group was not of the same sex as the other two groups.

TABLE V

TOTAL HEART VOLUME AND HEART VOLUME PER SQUARE METER OF BODY SURFACE AT DIFFERENT AGES

	AGE (YR.)	HEART VOLUME		
		C.C.	C.C./M^2.	$M \mp 2\sigma$ C.C./M^2.
12 girls	12–14	417	315	255–375
70 men	21–30	701	372	254–490
31 men	32–47	750	395	303–486

SUMMARY

We have determined by simultaneous roentgenograms, in two projections at right angles, values for the volume of the heart in 101 healthy men, aged from 21 to 47 years, and found that the normal heart volume varies between 7.0 and 13.0 c.c. per kilogram body weight and between 250 and 490 c.c. per m^2 of body surface.

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FOLLOW-UP STUDY OF SYSTOLIC MURMURS*

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THE systolic murmur, which had so long been considered insignificant, has again gained a position of importance. Those of us who examined the "command for cardiovascular disease" during the last war can remember that we were instructed to disregard the systolic murmur. It was the accepted teaching during that period that so-called functional or nonpathologic murmurs were common in normal, healthy individuals. It was taught that mitral regurgitation rarely occurred without stenosis and that the systolic murmur alone did not mean mitral disease. Some believed that the use of the stethoscope had done more harm than good. This was in contrast to the point of view held in the period just after the discovery of the stethoscope. At that time, every murmur in the heart was considered indicative of organic heart disease. Systolic murmurs at the apex were believed to be diagnostic of mitral regurgitation. In the past few years, however, the pendulum has made another wide sweep in the opposite direction and we are now advised that almost every systolic murmur is of significance and needs to be carefully studied; that while nonpathologic murmurs do exist, they are much fewer in number than formerly believed. We are told that, by careful physical examination, it will be found that most of these murmurs mean either organic heart disease or are indicative of heart abnormalities secondary to such conditions as anemia, hyperthyroidism, or hypertension.[1] The two most recent reports on the systolic murmur, by White[2] and Levine,[1] were based on a single examination of a large number of individuals with no follow-up study.

At the Lymanhurst Heart Clinic we have been able to carry on a follow-up study on 102 patients on whom an original diagnosis of nonpathologic murmur was made. The initial examination as well as all subsequent follow-up examinations were made by the writer. This is a select group, in that every effort was made to exclude all patients with possible early organic heart disease. The criteria for making a diagnosis of nonpathologic murmur were as follows: (1) No history of rheumatic infection; (2) murmur in the heart not characteristic of congenital heart disease; (3) heart normal in size and contour, as shown by postero-anterior and lateral roentgenograms and by fluoroscopy when indicated; (4) no evidence of anemia or hyperthyroidism.

Patients who gave a history of rheumatic infection but whose hearts were normal roentgenologically were classified as having "potential

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heart disease'' whether they had a systolic murmur or not, and were not included in this study.

Those who had loud, harsh murmurs at the base of the heart considered characteristic of congenital heart disease were excluded even though the heart was found to be normal in size and contour.

Although this group is small, it consists of patients who were carefully selected and in whom a diagnosis of nonpathologic murmur was based on a careful history and physical examination, including roentgenologic studies, electrocardiograms, and other necessary laboratory procedures. These patients had been referred to the clinic for cardiac examination because a murmur had been found in the heart either by the school physician or family doctor. In many of them a previous diagnosis of leakage of the heart had been made, and a number of them had been refused life insurance or had been ''rated up'' because of a heart murmur.

TABLE I

AGE OF PATIENTS

YEARS OF AGE	FIRST EXAMINATION		TOTAL	LAST EXAMINATION		TOTAL
	MALE	FEMALE		MALE	FEMALE	
5-10	39 (65.0)	23 (35.9)	62 (60.8)	9 (40.9)	12 (54.5)	21 (20.6)
11-15	21 (50.0)	19 (45.2)	40 (39.2)	23 (69.7)	10 (29.4)	33 (32.4)
16-20				24 (53.3)	19 (44.2)	43 (42.2)
21-25				4 (80.0)	1 (20.0)	5 (4.9)
Total	60 (58.8)	42 (41.2)	102	60 (58.8)	42 (41.2)	102

Age of Patients.—Table I indicates that a total of 102 patients were studied, of whom sixty were males and forty-two females. The ages of these patients at the first and last examinations are given. The common belief that functional murmurs are more common in the female is not borne out by these figures. About one-half of the patients were followed from childhood to early adult life.

TABLE II

YEARS FOLLOWED WITH RELATION TO CHANGE IN DIAGNOSIS

(Average Number of Years Followed 4.6)

YEARS FOLLOWED	NUMBER OF CASES	NO CHANGE	NO HEART DISEASE	CONGENITAL HEART DISEASE	RHEUMATIC HEART DISEASE	POSSIBLE EARLY HYPERTENSION
2- 4	61 (59.8)	47 (77.0)	11 (18.0)	2 (3.3)	1 (1.6)	
5- 8	31 (30.4)	24 (77.4)	4 (12.9)			3 (9.7)
9-12	10 (9.8)	5 (50.0)	2 (20.0)	1 (10.0)		2 (20.0)
Total	102	76 (74.7)	17 (16.7)	3 (2.9)	1 (1.0)	5 (4.9)

Number of Years Followed and Change of Diagnosis.—Table II correlates the number of patients in whom a change of diagnosis was made with the number of years observed. In seventy-six children the murmur persisted throughout, in seventeen the murmur disappeared, while in three instances the diagnosis was changed to ''probable congenital

heart disease.'' This change in diagnosis was based both on an alteration in the intensity of the murmur and roentgenologic changes. It is of interest to consider somewhat in detail these three patients. The first patient was initially examined in 1928, when he was 8 years of age. At that time a localized systolic murmur was found at the apex. The roentgenologic examination revealed that the heart was normal in size and contour. The patient was not examined again until 1932, when the same murmur was again heard, but on roentgenologic examination the heart was found to be moderately enlarged. The contour was considered atypical. The electrocardiogram was normal but a definite diagnosis could not be made. The patient was examined each year thereafter until February, 1938. It was not until 1938 that a definite diagnosis of congenital heart disease was made. The second patient was first examined in 1935, when a short harsh murmur was heard along the left border of the sternum. The murmur was thought to vary considerably with respiration and was not transmitted. A diagnosis of nonpathologic murmur was made. The patient was not seen again until February, 1938, when, as a result of clinical and roentgenologic examinations, a fairly definite diagnosis of congenital heart disease was made. In this case, the roentgenologic examination revealed that the heart was normal in size. There was, however, a moderate enlargement of the pulmonary artery, especially well demonstrated on fluoroscopic examination, which was thought to be quite characteristic of congenital heart disease. In the third case, the patient was first examined in 1935, when a systolic murmur was heard over the base of the heart. The murmur was then thought to be of no importance. He was again examined in 1936. The same murmur was heard and it was still considered nonpathologic in nature. Roentgenologic examination revealed that the heart was normal in size and contour on both occasions. However, in April, 1938, when the patient was re-examined, the murmur had become much louder and much more prolonged and was heard along the left border of the sternum as well as at the apex. The teleoroentgenogram and esophagram revealed that the heart was normal in size and contour. However, on fluoroscopy, there was slight enlargement of the pulmonary artery, and this finding, together with the increased length and intensity of the murmur, was considered at least suggestive of congenital heart disease.

Twenty-nine of these patients when originally examined gave a history of so-called ''growing pains'' which we considered nonrheumatic in nature. Many such patients are being considered rheumatic because of ''growing pains'' alone, and no attempt is made to differentiate such patients from those suffering from subacute rheumatic fever. It has been my contention[3] that such a differentiation is possible by careful clinical analysis. The results of this follow-up study tend to substantiate my point of view, as none of these twenty-nine patients subsequently

developed rheumatic heart disease. The one patient who developed aortic regurgitation gave no history of rheumatic fever or of "growing pains." He was examined first in 1935, when a localized systolic murmur was heard at the apex. This was considered functional in nature. On repeated examinations, from 1935 to 1937, the same murmur was heard, while roentgenologic studies revealed that the heart was normal in size and contour. In 1938, however, a faint diastolic murmur was heard along the left border of the sternum and the heart was slightly enlarged; the contour suggested early left ventricular enlargement.

In five patients the diagnosis was changed to "possible early hypertension." The systolic blood pressure was between 140 and 150 mm. Hg in four of them; while in one case the blood pressure was 180/94. These patients were all males, and their ages ranged from 17 to 26 at the final examination. At first glance this might appear to be of significance, but it has been observed[4] that of any group of young people followed over a period of years 4 to 5 per cent will show mild hypertension by the time they reach early adult life.

Of the 102 cases in which nonpathologic murmur was originally diagnosed, in one instance a definite diagnosis of congenital heart disease was finally made, while in two instances it was concluded that a congenital lesion was possibly present. In one case aortic regurgitation developed; while in five instances early hypertension seemingly occurred. If these last five subjects are considered normal and the two questionable congenital lesions are excluded, it can be concluded that a correct diagnosis of nonpathologic murmur was made in 98 per cent of our cases.

Location and Intensity of Murmurs.—It has been pointed out by a number of investigators that the murmurs of greater intensity and length are much more likely to be significant of organic heart disease. Levine,[1] in his recent report, states that murmurs which were found to be functional in nature were usually short and of slight intensity. It is of interest, then, to classify the murmurs in the patients observed in this study. We have used an arbitrary classification of one plus to five plus, similar to Levine's classification; a one-plus murmur indicates a systolic murmur heard well into systole, but short and not intense. These were definite murmurs and not simply roughening of the first sound. The two-plus murmur is somewhat louder and longer, etc., until, by a five-plus murmur, is meant one which is very loud and very rasping, such as is heard most commonly in congenital heart disease.

Fig. 1 reveals that our findings tend to corroborate the point of view that the great majority of murmurs found to be nonpathologic in nature are of slight intensity.

Change in Diagnosis with Relation to Intensity and Transmission of Murmurs.—It seemed of value to determine whether or not the intensity and transmission of murmurs were significant in relation to the change in

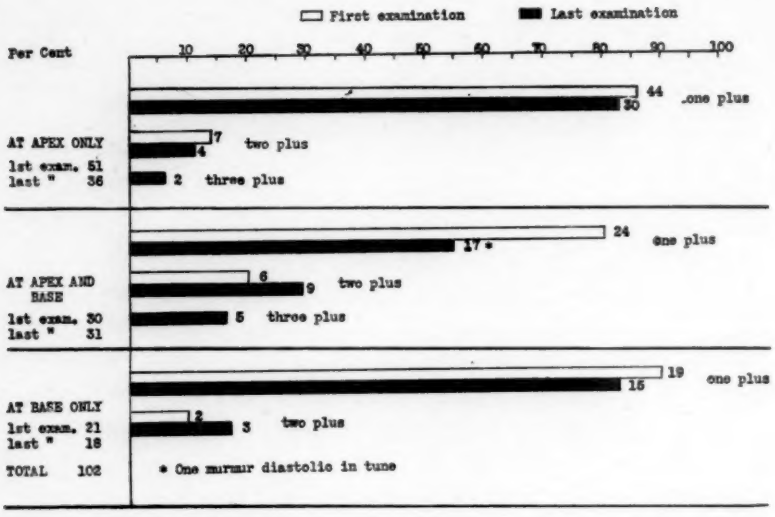

Fig. 1.—Location and intensity of murmur. Intensity of murmurs rated one-plus to five-plus.

diagnosis. It has long been taught that murmurs of greater intensity which were well transmitted into the axilla or heard through to the back and those which obscured the first sound were most probably due to organic heart disease. It is to be noted (Fig. 2) that in almost every

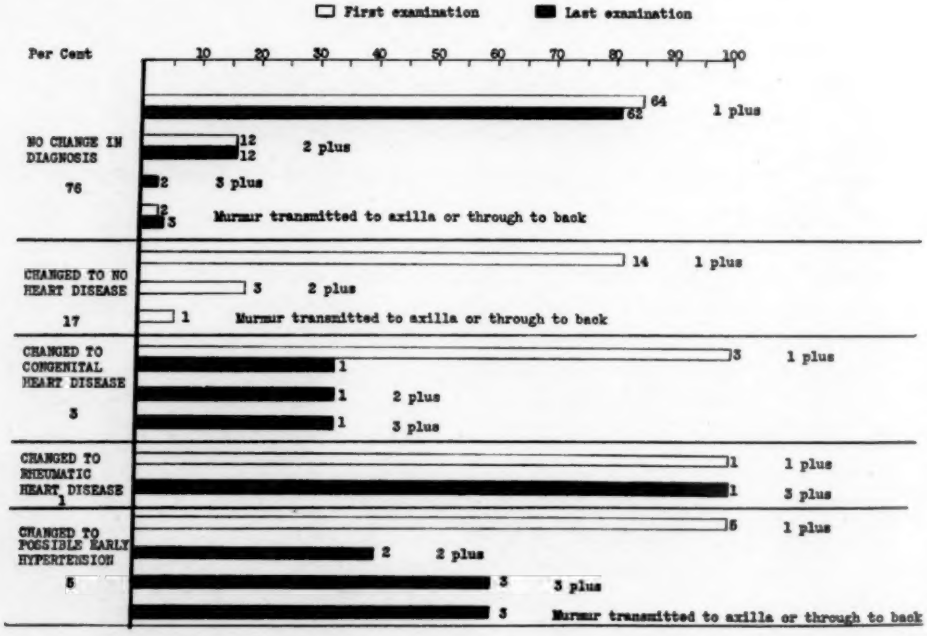

Fig. 2.—Change in diagnosis in relation to intensity and transmission of murmur. Intensity of murmurs rated one-plus to five-plus.

instance in which the diagnosis was changed to organic heart disease or possible early hypertension, the murmur became greater in intensity and was heard in the axilla or through to the back. These findings would tend to indicate that murmurs of greater intensity are more suggestive of organic heart disease and that most functional systolic murmurs are short, do not obscure the first sound, and are rarely heard in the axilla or through to the back.

Roentgenologic Studies.—Probably one of the most important methods of differentiating between murmurs of organic nature and those considered functional is the roentgenologic examination, including fluoroscopy. For a number of years in our clinic it has been customary to obtain at least a teleoroentgenogram of every patient who reported, whether or not clinical evidence of heart disease was noted. We have been able to keep down the expense of this procedure by the use of paper films. These films have proved entirely satisfactory as far as our work is concerned.

At the first examination all but one of these patients had a teleoroentgenogram. Twenty-two of them had lateral films, with the esophagus filled with barium, as well. The hearts of all of them were considered normal in size and contour. At subsequent, and especially at the last examination, every patient had posteroanterior and lateral films taken and forty-two were fluoroscoped.

The importance of fluoroscopy as well as oblique films of the heart has been stressed in recent years.[5] There can be no question that free use of the roentgenologic method will aid greatly in cardiac diagnosis. In children and young adults, however, considerable experience is necessary in interpreting oblique films. This is especially true of fluoroscopy. As is well known, the heart in the young appears relatively large and, in many instances, it is difficult to decide definitely whether or not a slight enlargement of the conus pulmonus or pulmonary artery is present. It is my impression that roentgenologic studies of the heart are more efficiently done and prove of more practical value when carried out by the cardiologist rather than the roentgenologist. It is significant, too, that, in sixteen of the 102 patients, at the first roentgenologic examination mention was made of "possible slight cardiac enlargement" or "possible slight enlargement of the conus pulmonus or pulmonary artery," and yet follow-up study showed that the heart was normal in every one of these patients. The cardiothoracic ratio so commonly used at present in measuring the heart is notoriously incorrect. This is especially true in growing children. In children with normal hearts, at one age the transverse diameter of the heart may be slightly over 50 per cent of the total transverse diameter of the chest, and yet on subsequent examinations, with no disease developing in the heart, the size of the heart will be found normal.

The electrocardiogram was found to be of little value in differentiating between functional and organic murmurs. At the first examination, eighteen were obtained, while at the last examination fifty-seven were taken, and in none of them were abnormalities found.

There have been a number of recent studies indicating that the functional systolic murmur is commonly produced by increased velocity of blood flow. It is well known that with tachycardia murmurs often appear at the apex and base of the heart and commonly disappear when the heart slows down. In our group of cases, however, only in nine patients was a rapid heart rate noted. It has also been stated that underweight individuals whose chests tend to be flat are those who most commonly present nonpathologic murmurs. In the great majority of our patients the height and weight were within normal limits.

DISCUSSION

This study indicates that every systolic murmur is of importance and needs to be carefully considered before concluding that it is nonpathologic. It also corroborates the point of view that short murmurs of slight intensity, whether they occur at the apex or base of the heart, are most probably nonpathologic, especially when they are not well transmitted. Follow-up examinations show, however, that with careful history taking and complete physical examinations, including roentgenologic studies, a diagnosis of nonpathologic murmur can be made with a high degree of accuracy.

CONCLUSIONS

(1) One hundred two patients with nonpathologic systolic murmurs were followed over a period of years, and the original diagnosis was found to be correct in 98 per cent.

(2) Murmurs of nonpathologic nature are most likely to be short and of slight intensity and are not well transmitted.

(3) A diagnosis of nonpathologic murmur can be made with a high degree of accuracy if careful histories are taken and complete physical examinations, including, especially, roentgenologic studies, are made.

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TRANSIENT BUNDLE BRANCH BLOCK AND OTHER ELECTROCARDIOGRAPHIC CHANGES IN PULMONARY EMBOLISM*

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REPORTS of studies concerning the electrocardiographic changes in cases of pulmonary embolism have been appearing in the medical literature with increasing frequency. The purpose actuating these studies has been the search for characteristic changes which might aid in the differentiation of this condition from coronary occlusion, a differentiation which has often been the source of great difficulty to the practitioner. The clinical features so often relied upon for the diagnosis of coronary occlusion may be duplicated in practically every respect by pulmonary embolism. This is true of the sudden onset with collapse, dyspnea, and vomiting, the substernal pain, the drop in blood pressure, and the fever and leucocytosis. Furthermore, a pericardial friction rub may be heard in pulmonary embolism, due presumably to dilatation of the pulmonary artery and conus, thus leading to confusion with the friction rub so often heard in anterior cardiac infarction. The hemoptysis and pleural friction rub classically associated with pulmonary embolism are frequently absent in that condition.

Differentiation of the two conditions by means of the electrocardiogram has not yet been established on a solid foundation. McGinn and White,[1] in discussing "the acute cor pulmonale" of pulmonary embolism, demonstrated electrocardiographic changes of a temporary nature, consisting in the presence of a Q-wave and late inversion of the T-wave in Lead III, a rather low origin of the T-wave with a gradual, staircase ascent of the ST interval in Lead II, a prominent S-wave and a slightly low origin of the T-wave in Lead I, and an upright T-wave (with inverted P- and QRS-waves) in Lead IV. Such changes in the standard electrocardiogram simulate those seen in infarction of the diaphragmatic surface of the heart (the so-called Q_3T_3 type of electrocardiogram). These authors believed that Lead IV would serve for differentiation inasmuch as this lead may show an abnormal T-wave, whereas in infarction of the diaphragmatic surface of the heart T_4 is usually normal. Barnes[2] was in accord with McGinn and White concerning the importance of Lead IV, and emphasized the diagnostic importance of the large S_1 in pulmonary embolism, a deflection usually absent, or very small, in the T_3 type of electrocardiogram of coronary thrombosis.

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Love and Brugler,[3] however, in a recently reported study of five cases of pulmonary embolism, pointed out that S_1 was present in only two of their cases, and that T_4 was often of no value in the differentiation from coronary thrombosis. In two of their cases, marked S-T segment depression was present in Lead I. They have concluded that there is no electrocardiogram characteristic of pulmonary infarction.

The purpose of this communication is to report three cases of pulmonary embolism, observed at Temple University Hospital, in which striking serial electrocardiographic changes were observed. A study of these electrocardiographic changes reveals further information which may be of value in clarifying the sequence of electrocardiographic events associated with acute pulmonary disorders, and make possible a more accurate means of differentiation from coronary occlusion.

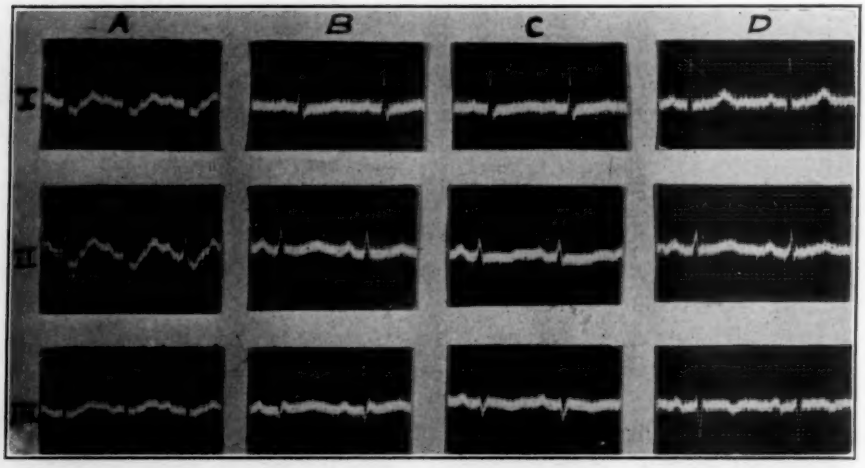

Fig. 1.—Serial electrocardiograms in Case 1. *A*, Two hours after onset of symptoms of pulmonary embolism; *B*, twelve hours after onset; *C*, forty-eight hours after onset; *D*, twenty days after onset. For description, see text.

CASE 1.—J. M., a man 69 years old, was admitted to Temple University Hospital Feb. 7, 1936, for treatment of an intracapsular fracture of the left femur which had been incurred three days previously. History and examination were entirely negative except for the findings relative to the fracture. On Feb. 11, 1936, a Smith-Peterson nail was introduced, under spinal anesthesia, to secure fixation of the fragments. The patient's postoperative condition was good. On Mar. 3, 1936, while sitting in bed, he suddenly experienced severe dyspnea, became markedly cyanotic, and perspired profusely. There was no pain. The blood pressure was 68/40. Stimulants were administered and the patient placed in an oxygen tent. His general condition improved rapidly, and the following day the blood pressure was 116/70. Electrocardiograms were taken at intervals of two hours, twelve hours, forty-eight hours, and twenty days after the attack. These are shown in Fig. 1. A roentgenogram of the chest taken three days after the attack showed an area of abnormal density in the right lung field.

CASE 2.—D. P., a woman 56 years of age, was admitted to Temple University Hospital July 24, 1934, complaining of severe pain in the right upper quadrant of the abdomen. She had had an attack of gall bladder colic two years previously, but the

history was otherwise negative. Operation on the day of admission showed acute pancreatitis and cholangitis. A cholecystostomy was done, and the abdomen drained. The postoperative course was stormy. On the twenty-second postoperative day she experienced sudden, severe, precordial pain and oppression, dyspnea, and anxiety. There were marked cyanosis, circumoral pallor, a rapid, thready pulse, and profuse perspiration. The blood pressure was 84/60. Recovery from this attack was

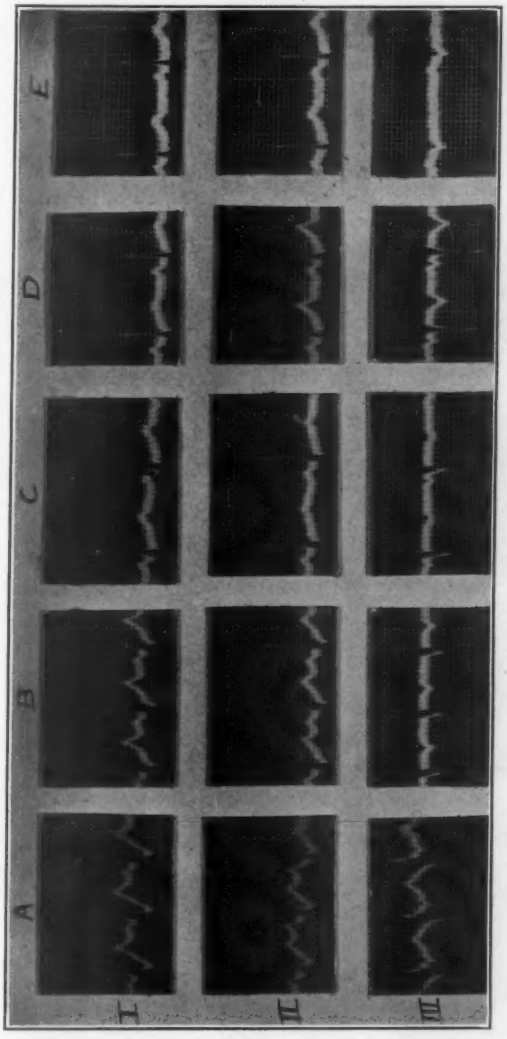

Fig. 2.—Serial electrocardiograms in Case 2. *A*, Taken within two hours after onset of symptoms of pulmonary embolism; *B*, five hours after onset; *C*, twenty-two hours after onset; *D*, five days after onset; *E*, three years later. For description, see text.

very slow, and was later complicated by the development of a left-sided perinephritic abscess which was drained on Sept. 11, 1934. Eventually the patient made a complete recovery, and on a recent visit to the hospital (Nov. 15, 1937) a complete examination, including thorough cardiac study, was entirely negative, except for the possibility of residual gall bladder disease. Electrocardiograms taken at intervals following the attack of pulmonary embolism and again at the time of the recent examination are reproduced in Fig. 2. The diagnosis of pulmonary infarction was substantiated in this case by the roentgenologic findings soon after the attack.

CASE 3.—M. B., a woman 54 years of age, was admitted to Temple University Hospital April 28, 1938, complaining of pain in the left loin and hematuria. Examination was negative except for obesity and a blood pressure reading of 170/90. A left-sided pyelolithotomy was performed on April 30, 1938. There were no unusual postoperative developments until the twelfth postoperative day, when the patient suddenly felt weak and cold, and noted tightness under the sternum. She was markedly dyspneic, cyanotic, and apprehensive. There was profuse perspiration. The pulse was regular and its rate was 120 a minute. Crepitant râles were heard at the base of the right lung. The blood pressure was 132/84. The patient's condition gradually improved, and by May 5, 1938, the blood pressure had risen to the preoperative level. Pleural pain over the base of the right lung developed on May 14, 1938, and persisted until May 25, 1938. The râles were continuously present throughout this period, together with dullness and diminished breath and voice sounds over the right lower lobe. The patient made an uneventful recovery following this and was discharged on June 2, 1938, in good condition.

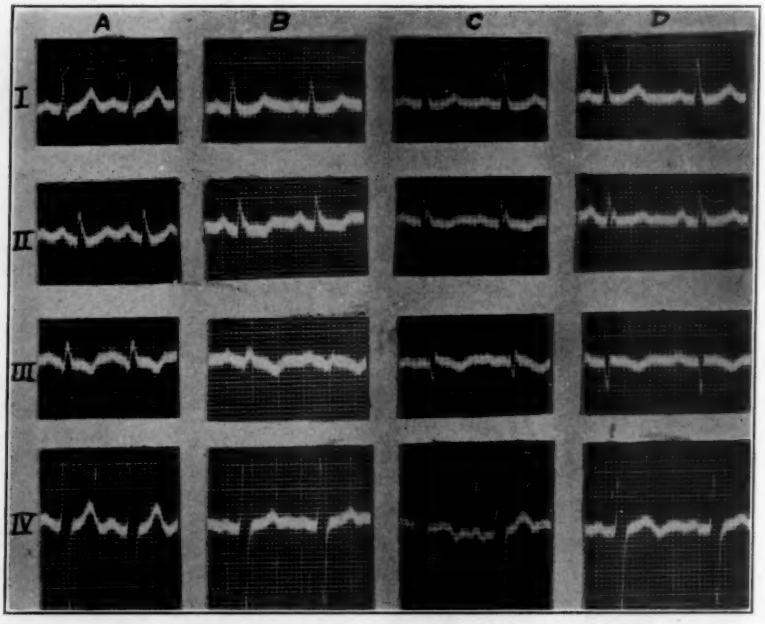

Fig. 3.—Serial electrocardiograms in Case 3. *A*, Taken six hours after onset of symptoms of pulmonary embolism; *B*, twenty-four hours after onset; *C*, six days after onset; *D*, twenty days after onset. In Lead IV relative negativity of the anterior electrode is represented by a downward deflection. For description, see text.

The first electrocardiogram was not taken in this case until six hours after the onset of symptoms of embolism. This electrocardiogram, together with subsequent tracings, is reproduced in Fig. 3. The patient was given 1.3 gm. of digitalis in the interval between curves *A* and *B*. No digitalis was given following this.

DISCUSSION OF ELECTROCARDIOGRAMS

For purposes of convenience and clarity in description, the discussion of the electrocardiographic changes in the cases above reported will be divided into the early and later changes. The early changes are those which appear within an hour or two after onset; while the later changes,

which consist in a gradual reversion of the early changes toward the normal, are seen some hours later, and extend over a period of days. It will be apparent from the discussion that the serial changes are much more rapid in their progression than are those following coronary occlusion.

Early Changes.—The early electrocardiograms in Cases 1 and 2 (Figs. 1*A* and 2*A*, respectively) were taken within two hours of the onset of pulmonary embolism. Intraventricular block is present in each, and is of the type shown by Wilson, et al.,[4] to be due to a conduction disturbance in the right bundle branch. In Case 1 the QRS interval measures 0.13 second, and in Case 2 it measures 0.12 second. In both instances there is an initial, narrow, upward spike, followed by a broad, U-shaped S-wave in Leads I and II. In Lead III in Case 2 there is a broad R-wave corresponding to the S-wave in the other two leads.

The majority of electrocardiograms published in the literature as examples of the changes occurring in pulmonary embolism are curves taken at longer intervals following the onset of symptoms than are these first curves. One curve obtained by McGinn and White, however, was taken two hours after the attack. This electrocardiogram showed a rather broad, somewhat rounded S-wave in Lead I, similar in contour to that seen in our cases, but without prolongation of the QRS interval beyond normal limits. This curve would seem to represent a stage of transition between our early changes and those to be described as later changes.

In two of the five cases reported by Love and Brugler there may have been early changes, but the exact time at which the electrocardiograms were taken is not mentioned in their report. The electrocardiograms in these two cases do not show QRS prolongation, but, instead, marked displacement of the S-T segment in all leads.

Pick[5] has published an electrocardiogram taken before, and another taken a few minutes after, the onset of pulmonary embolism. The electrocardiogram before the attack showed a QRS interval of 0.08 second, and was normal except for slight left axis deviation, but the curve taken immediately after the attack showed right bundle branch block with broad S-waves in Leads I and II and a QRS interval of 0.12 second. The patient died four hours after the onset of symptoms. Postmortem examination showed an embolus involving the main stem of the pulmonary artery. No coronary or myocardial disease was found.

In another case seen by one of us (T. M. D.) at the Desert Sanatorium of Southern Arizona, but not reported in detail in this article, right bundle branch block was observed in the electrocardiogram of a patient with pulmonary tuberculosis who had developed thrombotic occlusion of the artery to the middle lobe of the right lung with ensuing infarction and abscess formation in that lobe. The clinical picture with the onset of the infarction was similar to that of coronary occlusion, and included

the presence of a pericardial friction rub on the day of onset of symptoms. The electrocardiogram, taken within two hours of the onset of the attack, showed a broad S-wave in Lead I, and a QRS interval of 0.1 second. At post-mortem examination no evidence of coronary or myocardial disease was found.

Later Changes.—The transient character of the bundle branch conduction disturbance in cases of pulmonary embolism in which the patient recovers is demonstrated by its total absence in curves taken five hours (Case 2, Fig. 2*B*), and twelve hours (Case 1, Fig. 1*B*) after onset. The QRS complex is of normal duration in both, and the broad U-shaped S-wave in Lead I has been supplanted by a sharp, narrow deflection. The staircase ascent of the S-T segment is now well demonstrated in Case 2. This latter phenomenon is also of short duration, however, having given way to a more normal contour in the curve taken twenty-two hours after onset (Fig. 2*C*). In Case 1 the staircase ascent of the S-T segment was not present in the second curve, but this may be due to the fact that it was taken at a longer interval after onset (twelve hours) than was the second curve in Case 2, or the first curves of McGinn and White.

An important feature in the later serial changes is the eventual disappearance of the S-wave in Lead I. In Case 1 it had disappeared in the curve taken twenty days after the attack. In Case 2 it was still present in the curve taken five days after onset, but had disappeared in the curve taken three years later. It is possible, of course, that the disappearance in this case may have taken place at a time corresponding to that in Case 1, but interval electrocardiograms are lacking to demonstrate this point. In Case 3 the S-wave in Lead I had disappeared in the curve taken twenty-four hours after the attack (Fig. 3*B*).

The series of electrocardiograms in Case 3 (Fig. 3) lacks a curve taken within six hours after the onset of pulmonary infarction, when the intraventricular conduction disturbance in Cases 1 and 2 was demonstrated. The first curve in this series corresponds in contour with Fig. 2*B* of Case 2, and was taken at a similar interval after onset of symptoms. It presents an S-wave in Lead I, a staircase ascent of the S-T segment in Lead I, and, in Lead III, a Q-wave with an inverted T-wave. In the second electrocardiogram, taken twenty-four hours after onset, and in the subsequent curves, the S-wave in Lead I is absent. The S-T changes in Leads I and II have been modified, probably by reason of the digitalis received by the patient in the interval between the taking of the first and second curves.

Lead IV was not taken with sufficient frequency in this series of cases to allow any conclusions to be drawn concerning its characteristics. In Case 3, the only one in which this lead was used throughout, the first curve showed a positive, or normal, T_4. This was modified somewhat in the later curves, possibly by the effect of digitalis. In this case

Lead IV would have been of no value in differentiating between pulmonary embolism and coronary occlusion. Unfortunately this lead was not taken in either Case 1 or Case 2 at a time when the intraventricular conduction disturbance was present.

COMMENT

A review of the standard leads in the three cases reported, together with a study of curves published by others, leads us to the opinion that there is a rapid series of electrocardiographic changes associated with acute pulmonary heart disease which may be summarized as follows:

Early.—(1) Intraventricular block of the right bundle branch type, with a broad, shallow S-wave in Lead I and II; (2) marked depression of the S-T segment in Leads I and II may be present, as in the cases reported by Love and Brugler.

Later.—(1) Re-establishment of normal intraventricular conduction associated with the supplanting of the broad S-wave in Leads I and II by a wave of sharp, narrow contour; (2) a sloping ascent of the S-T segment in Leads I and II; (3) a Q-wave and inverted T-wave in Lead III.

Subsequently.—A disappearance of the above changes by a gradual process of reversion toward the normal, except for the persistence, in some, of the changes in Lead III.

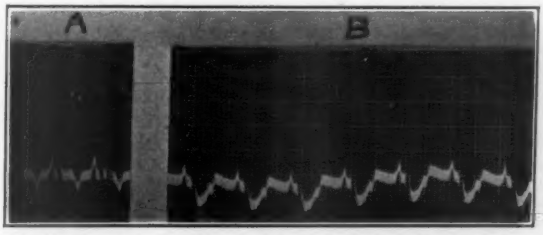

Fig. 4.—Electrocardiogram (Lead II) of a dog before (*A*) and after (*B*) the rapid injection of 30 c.c. of air into the femoral vein.

This series of changes, with its dramatic onset in temporary right bundle branch block and the subsequent reversion to normal, we have never seen in coronary occlusion, nor have we seen it in any condition other than acute pulmonary heart disease. It is true that atypical right bundle branch block of the type described may appear following the onset of coronary occlusion, but, when such is the case, the conduction disturbance does not rapidly subside with a gradual narrowing and eventual complete disappearance of the S-wave in Lead I. We feel that the serial changes described are characteristic of acute pulmonary heart disease, and may prove to be an important diagnostic aid. It is to be emphasized, however, that the most significant features appear very soon after the onset of the condition and disappear very rapidly. In order

to be of the greatest diagnostic value, therefore, the electrocardiographic study should be begun within the first hour or two after the onset of symptoms in a case of suspected pulmonary embolism.

The mechanism responsible for these electrocardiographic changes is not understood. Experimental studies[6] show that changes in the QRS complex identical with those seen in Fig. 1*A* and Fig. 2*A* may be produced in dogs by air embolism from the systemic venous circulation (Fig. 4). These changes come on at a time when there is noted, in open chest experiments, a sudden dilatation of the right ventricle following the injection of the air. Evidence will be published to show that, in these experiments, anoxemia was not responsible for the changes induced by the air embolism. Whether sudden dilatation of the right ventricle can be held as the only factor in their production will require further experimental study.

SUMMARY

Transitory electrocardiographic changes which have their onset in right bundle branch block and occur in association with pulmonary embolism are described and their diagnostic significance discussed. The importance of the very early conduction disturbance, occurring within a few hours of the onset of the condition, and the rapidity with which this disturbance regresses are emphasized.

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TUMORS OF THE HEART AND PERICARDIUM*†

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MANY references to tumors of the heart and pericardium are found in past writings, but most of these are concerned with isolated case reports. The prevailing impression is that tumors of the heart and pericardium are quite rare. In 298 autopsies on patients with malignant disease, Symmers[1] found discrete metastases in the heart in only five cases (1.6 per cent). Statistical studies of Kitain,[2] Janusz,[3] and others record only occasional cases in which there were myocardial metastases. In a recent review of the subject, Yater[4] lists numerous autopsy series that have been investigated in regard to the occurrence of cardiac metastases and concludes that tumors of the heart and pericardium are rare.

Since Yater's review, five additional series have been published. Lymburner[5] found fifty-two secondary and four primary tumors of the heart in 8,500 autopsies at the Mayo Clinic. Pollia and Gogol[6] studied 12,000 autopsies at the Los Angeles General Hospital and found 1,450 cases of malignant tumors with twenty-nine secondary tumors of the heart. Helwig[7] reported nine cases of tumor of the heart in 1,000 autopsies at St. Lukes' Hospital in Kansas City. Burke[8] reported fourteen metastatic tumors of the heart in 327 cases of known malignant disease. Willis,[9] in 323 autopsies on patients with malignant tumors of all kinds, found metastatic growths in the myocardium in twenty cases, an incidence of 6.2 per cent.

Among 1,082 cases of malignant disease appearing in a series of 11,100 consecutive post-mortem examinations performed at the Cleveland City Hospital during the past twenty years, the heart was involved by metastases in 79; the parietal pericardium in 61; the heart and parietal pericardium together in 22; and the heart or parietal pericardium, or both, in 118. These results are summarized in Table I.

In this study, sarcoma and lymphoblastoma* involved the heart and pericardium relatively more often than did carcinoma, but the number of cases of sarcoma and lymphoblastoma in the series is small, so that no definite conclusion can be made. Actually carcinoma accounted for most of the cases, as shown in Table II.

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*Under lymphoblastoma are included cases of lymphatic leucemia, lymphosarcoma, Hodgkin's Disease, and reticulum cell sarcoma.

TABLE I

INCIDENCE OF INVOLVEMENT OF THE HEART AND PERICARDIUM IN 1,082 CASES OF MALIGNANT DISEASE

	NUMBER OF CASES	PERCENTAGE OF 1,082 CASES OF MALIGNANT DISEASE
Heart	79	7.3
Parietal pericardium	61	5.7
Both heart and parietal pericardium	22	2.0
Heart or parietal pericardium or both	118	10.9

TABLE II

INCIDENCE OF INVOLVEMENT OF THE HEART AND PERICARDIUM BY CARCINOMA, SARCOMA, LYMPHOBLASTOMA, MYELOGENOUS LEUCEMIA, AND MIXED TUMORS

TUMOR TYPES	NO. OF CASES	METASTASES TO HEART	METASTASES TO PARIETAL PERICARDIUM	METASTASES TO HEART OR PARIETAL PERICARDIUM OR BOTH
Carcinoma	943	53	54	89
Sarcoma	61	11	5	13
Lymphoblastoma	57	13	1	14
Myelogenous leucemia	14	2	1	2
Mixed tumors	7	0	0	0
	1082	79	61	118

In the cases recorded in the literature, metastases to the heart and pericardium have occurred from neoplasms involving practically every organ of the body. The distribution of the primary tumors metastasizing to the heart and pericardium in our material is shown in Table III.

From Table III it is apparent that carcinoma of the bronchus and breast is of paramount importance as a source of secondary tumors of the heart and pericardium, the incidence of involvement being 35.6 per cent in both instances. Reticulum cell sarcoma, melanoma, lymphatic leucemia, and chloroma metastasized to the heart frequently (all 50 per cent or more), but the number of cases is too small to be of statistical significance.

Our observations show that true embolic metastasis via the coronary arteries was the most common mode of involvement of the heart. Direct extension from either a primary or secondary tumor in the lung or a secondary tumor in the mediastinal lymph nodes was next in frequency, and invasion through the lymphatics (retrograde in the case of the heart, Aubertin,[10] Wolf and Giet[11]) was the least common.

The most common mode of involvement of the parietal pericardium was by extension. Hematogenous metastasis was next in frequency, and lymphatic metastasis was least common. Table IV summarizes the findings in regard to the mode of involvement.

TABLE III

THE DISTRIBUTION OF ONE HUNDRED EIGHTEEN SECONDARY TUMORS OF THE HEART AND PERICARDIUM

PRIMARY TUMOR	NUMBER OF CASES	METASTASES TO HEART	METASTASES TO PARIETAL PERICARDIUM	METASTASES TO BOTH HEART AND PARIETAL PERICARDIUM	METASTASES TO HEART OR PARIETAL PERICARDIUM OR BOTH
Carcinoma of bronchus	115	30	26	15	41
Carcinoma of breast	45	3	13	0	16
Reticulum cell sarcoma	9	6	0	0	6
Melanoma	10	5	2	2	5
Lymphatic leucemia	11	6	0	0	6
Chloroma	3	2	0	0	2
Leiomyosarcoma	6	1	2	0	2
Carcinoma of bladder	25	0	1	0	1
Carcinoma of cervix	49	2	0	0	2
Carcinoma of colon	27	0	1	0	1
Carcinoma of esophagus	61	2	2	0	4
Carcinoma of kidney	19	3	1	1	3
Hypernephroma	12	1	0	0	1
Carcinoma of liver	21	2	1	0	3
Carcinoma of pharynx	9	1	0	0	1
Carcinoma of lip	5	1	0	0	1
Carcinoma of ovary	19	1	0	0	1
Carcinoma of pancreas	45	2	2	0	4
Carcinoma of prostate	56	0	2	0	2
Carcinoma of rectum	39	2	2	1	4
Carcinoma of stomach	201	1	1	0	2
Metastatic carcinoma (primary undetermined)	16	2	1	1	2
Neurofibrosarcoma	2	1	0	0	1
Retroperitoneal sarcoma	2	0	1	0	1
Liposarcoma	1	1	0	0	1
Round cell sarcoma	4	1	0	0	1
Lymphosarcoma	13	1	1	1	1
Hodgkin's Disease	22	0	1	0	1
Myelogenous leucemia	14	2	1	1	2
Miscellaneous*	221	0	0	0	0
	1082	79	61	22	118

*Refers to a variety of tumors which in this series did not metastasize to the heart or pericardium.

TABLE IV

THE FREQUENCY OF THE VARIOUS MODES OF INVOLVEMENT OF THE HEART AND PERICARDIUM BY SECONDARY TUMORS

MODE OF INVOLVEMENT	HEART	PARIETAL PERICARDIUM
Definitely hematogenous	37	8
Definitely extension	18	25
Definitely lymphatic	0	3
Probably hematogenous	5	6
Probably extension	1	2
Probably lymphatic	0	7
Combinations	4	2
Undetermined	14	8
	79	61

More secondary tumors occurred on the left side of the heart than on the right, but the difference was not great. It would seem that the two sides of the heart are almost equally susceptible (Lymburner,[5] Bodenheimer[12]). The frequency of involvement of the various portions of the heart by metastatic tumors is as follows:

Parietal pericardium	61
Right auricle	29
Right ventricle	31
Left auricle	29
Left ventricle	45
Septum	11
Undetermined*	6

As others have found, the endocardium was least often involved (thirty cases). The epicardium and myocardium were more commonly the site of secondary tumor with no significant difference between the two (epicardium sixty-two cases and myocardium fifty-five).

The gross appearance of the secondary tumor of the heart varied widely. In some cases there were discrete tumor nodules varying from 1 mm. to 2 cm. in diameter. In other cases there was diffuse infiltration. The pericardial tumors likewise varied widely in nature and extent. Histologically, the tumors followed the pattern of the primary neoplasm. In several instances, tumor cells were found in lymphatic channels, in the coronary arteries, and in thrombotic masses within the chambers of the heart.

The pericardium was the seat of an acute pathologic process in 22 per cent of the cases in this series. The condition of the pericardium in 118 cases of secondary tumors of the heart and pericardium was as follows:

Normal	89
Simple effusion	5
Bloody fluid	7
Purulent pericarditis	3
Serofibrinous pericarditis	11
Obliteration by tumor	1
Fibrous obliteration	2

However, patients dying of malignant disease without cardiac metastases occasionally show similar pericardial disease. For example, in a control series of 100 malignant tumors that did not involve the heart or pericardium, acute pericardial disease was found in 7 per cent. In both series the amount of pericardial fluid was frequently insufficient to be detected clinically. It appears from our observations that evidence of pericardial disease in a patient with a known malignant process is a valuable diagnostic sign of cardiac metastases, but not a pathognomonic one.

*This group consisted of cases in which the tumor was found microscopically but the location from which the section was taken was not specified.

In accordance with the experience of others, the majority of the patients in this series showed no demonstrable clinical evidence of cardiac disease. Seven patients exhibited myocardial insufficiency. In five cases there were abnormalities of the cardiac mechanism without cardiac failure. A control series of 100 malignant tumors that did not involve the heart or pericardium failed to show any cases of myocardial insufficiency, but did include two cases in which there were abnormalities of the cardiac mechanism. At autopsy the abnormal cardiac mechanism could not be explained. Accordingly, it appears that myocardial insufficiency developing without apparent cause in a patient with a known malignant process is an important clinical finding pointing to cardiac metastases, while abnormalities of the cardiac mechanism are a suggestive sign, but not a pathognomonic one. Such signs of tumor of the heart as heart block, symptoms referable to the location of the tumor other than heart block, and suggestive roentgenologic observations were not observed in our series.

In only one of these seven cases with myocardial insufficiency due to tumor involvement of the heart was the correct diagnosis made ante mortem. This patient showed both cardiac failure and hemorrhagic pericardial fluid. In this instance the ante-mortem diagnosis of carcinoma of the bronchus with metastases to the heart and pericardium was substantiated at autopsy. The entire heart was extensively involved by tumor. Both layers of the pericardium showed much tumor tissue and an organizing fibrinous pericarditis.

In the remaining six cases heart failure was evident. In three of these cases it was known that the patient had a malignant disease, but in no instance was the possibility considered that tumor involvement of the heart could be responsible for the myocardial insufficiency. At post-mortem examination in all these cases there was extensive involvement of the heart by tumor, with no other explanation for the myocardial insufficiency.

As has been stated, five patients with metastases to the heart showed abnormalities of the cardiac mechanism without cardiac failure. Three of these had carcinoma of the bronchus, diagnosed correctly clinically. One showed paroxysmal auricular fibrillation; one, paroxysmal auricular fibrillation and paroxysmal auricular tachycardia; and one, auricular flutter. In none of these cases was the possibility of cardiac metastases considered. At autopsy, in two of these cases there was severe involvement of the atria by tumor and in one the left ventricle was involved.

The fourth patient, who also had carcinoma of the bronchus, had several attacks of paroxysmal auricular fibrillation. The possibility of cardiac metastases was considered, but a definite clinical diagnosis could not be established. At autopsy, the right atrium was involved by tumor. However, the heart showed a rheumatic mitral stenosis, and whether the

paroxysmal fibrillation was due to the tumor involvement or the rheumatic heart disease could not be determined.

The fifth case was one of melanosarcoma of the eye with generalized metastases. The diagnosis was proved clinically by means of biopsy. The patient showed attacks of paroxysmal auricular fibrillation and the possibility of metastases to the heart was thought of but could not be established. At autopsy, tumor tissue involved the left atrium, left ventricle, and the pulmonary conus.

An analysis of the electrocardiograms from these cases of secondary tumors shows, in accordance with Siegel and Young[13] and others, that there is no configuration pathognomonic of tumor of the heart. The electrocardiographic changes depend principally on the situation of the tumor. In this series, auricular fibrillation, auricular premature contractions, and auricular flutter predominated, and at autopsy in these cases with one exception involvement of the atria was found.

SUMMARY

Among 1,082 cases of malignant disease appearing in a series of 11,100 consecutive post-mortem examinations performed at the Cleveland City Hospital during the past twenty years, the heart, including the pericardium, was involved by metastatic tumor in 118 cases, an incidence of 10.9 per cent. Carcinoma of the bronchus and the breast most often invaded the heart and pericardium and accounted for 48 per cent of the cases in this series.

The development of congestive failure without other apparent cause, in a patient with malignant disease, was the most important clinical finding pointing to cardiac metastasis.

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PREMATURE CLOSURE OF THE FORAMEN OVALE

Report of Two Cases

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IN THE extensive literature on congenital cardiac anomalies there is almost no mention of premature closure of the foramen ovale. Lehman,[1] in 1927, reviewed the subject and found reports of five cases. He added a case report and presented the following classification of the condition: "(1) Infants with marked edema at birth, (2) infants apparently normal at birth but dying with cyanosis within a few days, and (3) atypical cases modified by other major cardiac anomalies." Two cases which fall in the first group were reported by Tait,[2] in 1875, and Osler,[3] in 1880. Both infants were premature and stillborn. Vieussens,[4] Smith,[4] and Lehman reported cases which fall into the second group; and Vernon[4] reported one which was complicated by other anomalies and so belongs in the third group.

The reports by Tait and Osler are almost identical. In each case there was marked hydramnios during the latter part of pregnancy, followed by premature delivery of a stillborn infant. The placentas were large and edematous, and the infants were so large that delivery was difficult. There was severe generalized edema and a marked waxy pallor of the skin. In both infants the foramen ovale was closed by an overlapping membrane which could be pushed aside to allow the passage of a probe. There was also a widely patent ductus arteriosus in both. In Osler's case there was marked enlargement of the right auricle to 6.8 cm. in circumference, and also dilatation of the right ventricle and hypertrophy of its wall to 8 mm. in thickness. The ductus arteriosus was 1.6 cm. in circumference, as compared to an aorta of 1.7 cm. The liver measured 15.5 cm. by 7 cm., and nothing further was noted. Tait's report did not include measurements, but this author attempted to explain the findings on the basis of a cardiac anomaly which caused hindrance to the passage of blood from the right auricle, with subsequent engorgement of all the vessels in front of the auricle throughout the double circulation. He stated that hydramnios resulted from the engorgement of the placenta.[2]

Recently two cases have been seen at the University of Colorado School of Medicine. One falls definitely into the first group of Lehman's classification, and the other probably belongs in the second group, since the infant lived for eleven hours and developed cyanosis before death. The fact that marked edema was noted in this second case, and was doubtless present at birth, suggests, however, that Lehman's first two groupings are too arbitrary.

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REPORT OF CASES

CASE 1.—Baby F. *History:* The mother was a 19-year-old bipara and was reported to have a negative blood Wassermann reaction. A stillborn fetus weighing 2750 gm. and measuring 44 cm. in length was delivered spontaneously, and at birth was noted to be very edematous. No other history was available and the infant was sent to us for autopsy.

Fig. 1.—Drawing of the heart of Baby F (Case 1), showing foramen ovale with overlapping membrane and hypertrophic right auricle. *A*, Arrow traversing the foramen ovale; *B*, left auricle; *C*, left ventricle; *D*, right ventricle; *E*, right auricle (hypertrophic).

Necropsy Report (eight days after death): The body was noted to have a waxy pallor and to be extremely edematous externally, but was otherwise normally formed. On incision of the skin much watery fluid escaped, and all of the body cavities contained considerable sanguineous fluid. The thymus showed extreme involution. The lungs were atelectatic. There was a bilateral otitis media. In this case there was no other focus of infection, which is unusual in a stillborn infant, since the common source of an ear infection is infected amniotic fluid which is likely to penetrate the sinuses and the bronchi as well as the ears.

The heart and the liver showed the most interesting abnormalities. The heart weighed 25 gm. (after fixation). The right auricle was enlarged and was about equal in size to all of the remaining heart tissue; it had a firm, thickened wall. The tricuspid valve appeared slightly thickened but its orifice seemed to be of normal size. The remaining chambers and valves of the heart were normal except that the ductus

arteriosus was widely patent and the foramen ovale was entirely covered by a membrane which overlapped the opening on all sides. From the right auricle a probe approximately 3 mm. in diameter could be pushed into the left auricle by lifting the lower part of the overlapping membrane (Fig. 1). Microscopically the heart showed hypertrophy of the muscle of the right auricle.

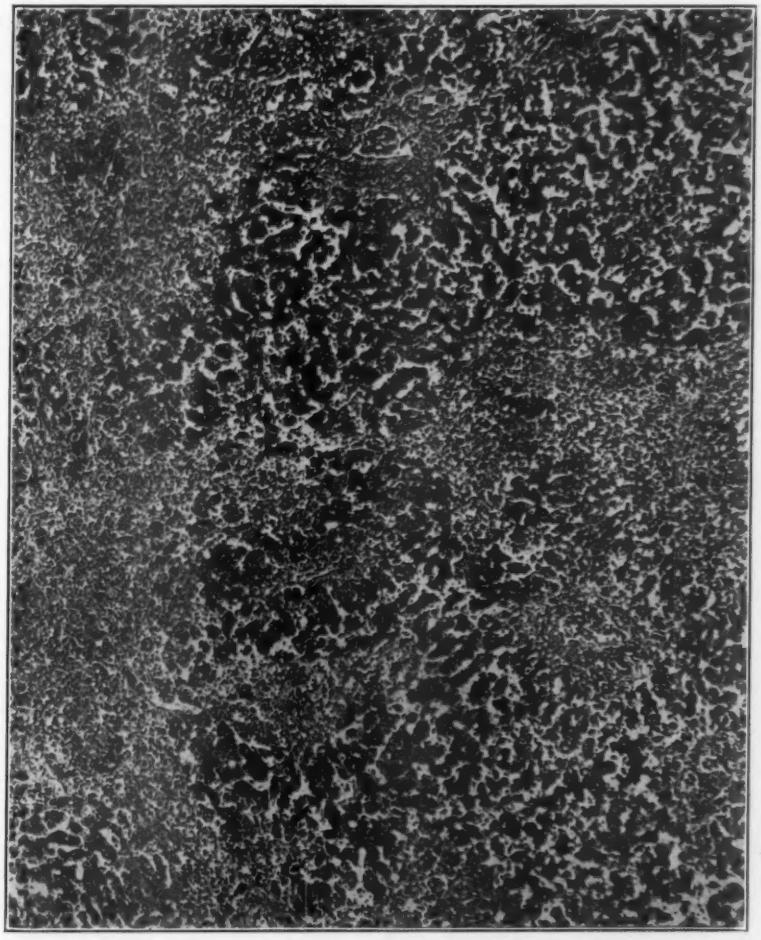

Fig. 2.—Photomicrograph (70×) of histologic section of liver, from Baby F (Case 1), showing patchy necrosis around the central veins.

The liver measured 8 by 4.5 by 3 cm. It was firmer than usual and showed some irregularity of the surface. Microscopically there was a slight increase in periportal connective tissue and a striking patchy central necrosis with atrophy of many of the liver cords. The condition was typical of a severe passive congestion (Fig. 2).

The placenta and membranes were not available.

CASE 2.—Baby A. *History:* The mother was a unipara, 19 years of age; the pregnancy was normal; at delivery there appeared to be a moderate hydramnios. The placenta was small and not edematous. The infant was 50 cm. long and weighed 2950 gm. He was difficult to resuscitate and much fluid poured from the nose and

mouth. This fluid had to be removed by repeated suction during all the time the infant lived. The baby never did well, finally became very cyanotic, and died eleven hours after birth.

Necropsy Report (five hours after death): The body was cyanotic and no rigor mortis was present. Generalized edema was present and the subcutaneous tissue was 1.5 cm. in thickness over the thorax and abdomen. Much free fluid escaped on incision of the skin. The subcutaneous tissue had a peculiar gelatinous appearance with fat particles suspended in it. The body cavities contained free fluid, the largest amount being present in the peritoneal cavity (about 20 c.c.).

Fig. 3.—Drawing of the heart of Baby A (Case 2), showing the foramen ovale with overlapping membrane. *A*, Arrow traversing the foramen ovale; *B*, left auricle; *C*, left ventricle; *D*, right ventricle (hypertrophic).

The heart weighed 30 gm.; the left ventricle was 5 mm. in thickness and the right ventricle 9 mm. The apex of the heart was formed by the right ventricle. The right auricle was not enlarged. Valve circumferences were as follows: tricuspid 3 cm., mitral 2.5 cm., pulmonic 2 cm., and aortic 1.5 cm. The ductus arteriosus measured 1.3 cm. in circumference. The foramen ovale was entirely covered by an overlapping membrane which could be pushed aside from the right auricle to admit a probe 4.5 mm. in diameter. The free edge of the membrane was anterior to the opening between the auricles (Fig. 3). Microscopically, the heart showed hypertrophy of the muscle of both right auricle and right ventricle.

The lungs showed marked edema, congestion, and atelectasis.

The liver weighed 81 gm. and was congested with blood. It showed a moderate amount of iron pigment microscopically, but was otherwise normal.

There was definite cerebral edema; the fluid was bloodtinged because of incomplete lacerations of the dura at the junction of the falx and tentorium.

DISCUSSION

The normal patent foramen ovale and ductus arteriosus of the fetus allow proper division of blood, and proportionate development of both sides of the heart (Fig. 4). Premature closure of the foramen ovale is prone to bring about certain secondary structural abnormalities. It may be assumed that variations in adaptability of different portions of the circulatory system may cause somewhat dissimilar end results. The various possibilities might be as follows: (1) The blood may be detoured through the pulmonary circuit, instead of going directly from the right

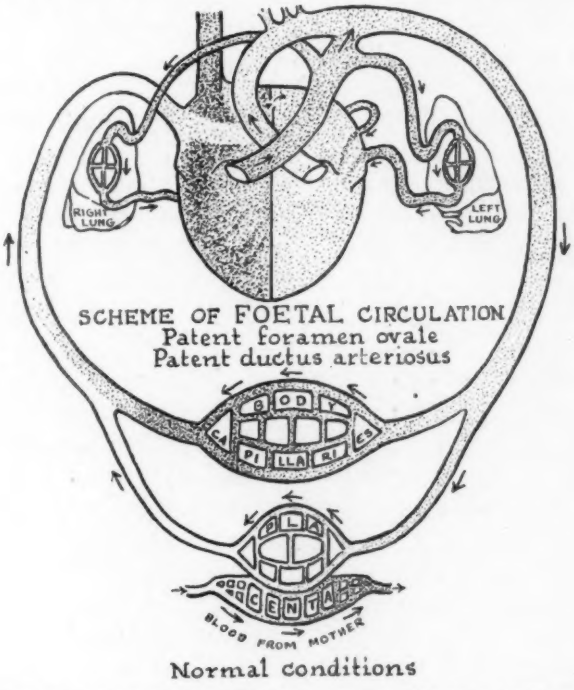

Fig. 4.—Diagram of normal fetal circulation. (From Abbott and Dawson, Internat. Clin. 4: 162, 1924).

to the left auricle. If the pulmonary circuit is adequate, or rapidly becomes adequate, a normal amount of blood can reach the left auricle and the heart may thus develop normally. Birth may then be followed by normal development of the infant. (2) If, on the other hand, the pulmonary circuit is not adequate, the excess blood may be shunted to the aorta by way of the ductus arteriosus. If this occurs the ductus may hypertrophy and the left auricle and left ventricle will receive less blood than normal, and so not develop *pari passu* with the right auricle and ventricle, which are being overloaded. (3) In case the fetal pulmonary circuit and ductus arteriosus are both inadequate to carry an increased load, the result will be the same as for any obstruction to free circulation, namely, the development of back pressure. This back pressure may

cause enlargement of the right auricle, as in Case 1, of the right ventricle, as in Case 2, and will eventually hinder the entire circulatory flow from the body and placenta, bringing about stasis and edema of the whole body and the placenta, as well as hydramnios. (4) In some cases it may be possible to maintain the circulation of the fetus in utero well enough to support life. However, in those cases in which the right side of the heart has enlarged disproportionately, the event of birth and the shutting off of the passage of blood through the ductus arteriosus will cause a larger volume of blood to go through the pulmonary circuit than can be pumped by the left side of the heart to the aorta. This will cause stasis in the lungs, with pulmonary edema and inadequate oxygenation, as well as failure of the left side of the heart.

Such an explanation would make clear the mechanism bringing about the syndromes mentioned by Lehman. The infants with edema at birth belong to the group with increasing obstruction during the latter part of fetal life, and the infants who are apparently normal at birth but soon develop cyanosis and die are those whose pulmonary stasis, edema, and left-sided heart failure develop at or after birth, partly because of the closure of the ductus arteriosus. Obviously, too, there might be gradations between these two extremes, as shown by the second case reported above.

The etiology of premature closure of the foramen ovale is probably purely developmental, the causative factor being an abnormality in the timing of the development of the intra-auricular septum. In Maude Abbott's discussion of congenital cardiac disease[5] the formation of this septum is shown to begin with the septum primum, which grows downward from the upper and posterior wall of the auricle as a sickle-shaped fold. This fold grows toward the ventricular cavity, and there is for a time a communication between the auricles which is known as the ostium primum. This primary membrane becomes very thin, and an opening forms in its upper and posterior part; this secondary opening continues to grow larger as the ostium primum becomes smaller and disappears.

Later, a secondary septum begins to form from the upper wall of the right auricle, grows downward, and comes to overlie the secondary opening in the primary septum, giving it a valvular character and transforming it into the foramen ovale. The ostium in the secondary membrane constitutes the foramen ovale and the valve is formed by the primary membrane. The foramen ovale is normally widely patent in fetal life, usually closes within twelve weeks after birth,[6] but may show a probe patency throughout the first year.[7] It may even persist, as a slit, in the adult (14 to 30 per cent of cases[5]). Persistent patency of the foramen ovale is considered to be caused either by pressure or pure growth arrest. The latter seems more likely in view of these cases in which the foramen ovale closes prematurely, since in them the pressure in the right auricle has certainly been increased, but the closure of the foramen has progressed with unusual rapidity.

Patten[7] stresses the point that congenital defects are as frequently due to overgrowth as to developmental arrest. The cases presented here give evidence in support of this view, as there appears to have been an overgrowth of either the overlapping valve or of the secondary membrane, bringing about an abnormal restriction in the size of the interatrial opening. It is not possible at the present time to determine which structure is primarily involved, as we have no measurements of the size of the secondary ostium in normal cases.

The foramen ovale at birth, in infants whose stage of development is similar to that in the cases presented here, has been found to vary from 7 mm. to 10 mm., as compared to 3 mm. in Case 1, and 4.5 mm. in Case 2. In Case 1, the edema in a stillborn infant denoted inadequate circulation with increasing obstruction during fetal life. In Case 2 the child was born alive, but developed symptoms soon after birth. Therefore, there appears to be a correlation between the degree of reduction in size of the foramen ovale and the extent of the pathologic changes observed in the two infants.

The discovery of cases of early closure of the foramen ovale is obviously possible only in stillborn or newborn infants. The presence of severe general edema should at all times be an indication for careful searching of the heart for an unusually small or absent intra-auricular opening, and for right-sided hypertrophy. Those infants who live for a short time and then become cyanotic and die, and in whom edema is noted, should be carefully examined for a definite right ventricular hypertrophy which can easily be differentiated from the right auricular dilatation so often seen.

SUMMARY

Two cases are presented in which there was partial premature closure of the foramen ovale, associated with fetal anasarca. This condition has been reported only a few times in the literature; all of the cases are similar.

A brief discussion of the mechanism and etiology of the condition is given.

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COARCTATION OF THE AORTA, NONCLINICAL TYPE, ASSOCIATED WITH A CONGENITALLY BICUSPID AORTIC VALVE

A Method for Its Recognition, With Report of a Case

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COARCTATION of the aorta, when it presents the classical clinical picture, affords no great difficulty of recognition during life. However, anatomic stenosis just at or below the insertion of the ductus arteriosus or its vestige may exist without hypertension and without the signs upon which the clinical diagnosis of coarctation is usually established. This is the result of the fact that various moderate degrees of narrowing of the isthmus may be present, and it is only in the pronounced grades of stenosis that physical signs may develop. Commonly, slight to even moderate degrees of constriction are missed at autopsy. The recognition of moderate, or "nonclinical," degrees of coarctation is of considerable clinical importance as regards prognosis because, even though the coarctation is not marked, there is still the possibility of associated congenital cardiovascular anomalies and the likelihood that subacute bacterial endocarditis may supervene. Maude Abbott[1] has shown that in approximately 40 per cent of cases coarctation is associated with other congenital anomalies of the heart, the most common being a bicuspid aortic valve, which was present in 25 per cent of the cases.

We are reporting a case of moderate coarctation of the aorta in which the clinical syndrome of coarctation was lacking; the associated anomaly was a congenitally bicuspid valve upon which was superimposed an infectious endocarditis. The correct diagnosis was made during life. In this regard we particularly wish to emphasize the importance of the radioscopic method in the examination of the heart and great vessels because it was by this method that coarctation was recognized in this case. In the left oblique radioscopic position the site of the constriction of the isthmus could be easily visualized (Fig. 1). This position (Fig. 2)[2a] has been found to be the most satisfactory one from which to study abnormalities of the aortic arch.[2b]

REPORT OF CASE

E. W., a white woman 31 years of age, a housewife, was admitted to the surgical service Aug. 24, 1937, complaining of weakness, loss of weight, intermittent fever, chills, dull pain in both flanks, and intermittent dysuria. These symptoms had been present since June, 1937.

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Patient had given birth to her last baby in February, 1937. This was an uneventful pregnancy. Beginning in the early part of June, 1937, the patient noted that she was losing weight and tiring easily. About this time she suffered an attack of pain in the left flank which persisted, with remissions and exacerbations, for about two weeks. She also noted that she was feverish on occasions and at times had definite chills. Following the initial attack of pain, the patient appeared to improve to some extent except for the persistence of nocturia and weakness. The weakness was so great as to confine her to bed nearly constantly.

Fig. 1.—Photograph of teleoroentgenogram in the left oblique position. The course of the aorta and the point of stenosis (indicated by arrow) are clearly shown. This point corresponds to the site of constriction shown in Fig. 4*a*. The opaque shadow lying anterior to, and parallel with, the aorta is the barium-filled esophagus.

Past history.—Patient stated that she had never been strong. Palpitation and tachycardia had been present for a number of years. Because of these symptoms she had consulted a physician five years before, and was told that she had leakage of the heart. There was no history of rheumatic fever, scarlet fever, or diphtheria. She had had five uneventful pregnancies with no resultant difficulties. She had never been short of breath until the onset of her present illness. She had been married for eleven years, had five children who were living and well, and her husband was living and well.

Physical examination.—On admission the temperature was 103°, the pulse rate 90, and the respiratory rate 20. Physical examination revealed an emaciated white

woman lying quietly in bed. There was no apparent distress. There was marked pallor of the skin with evidence of considerable recent loss of weight. The pupils were equal and reacted normally to light and in accommodation. Examination of the eyegrounds showed normal retinal vessels. The teeth were in good condition. The tonsils were enlarged. The thyroid gland was just palpable but not enlarged. There was no cervical adenopathy. A vigorous systolic pulsation and systolic thrill were noted in the suprasternal notch. The heart was not enlarged to percussion. The heart sounds over the apex were clear and slightly accentuated. A systolic murmur, soft and blowing in character, was heard over the apex. Over the aortic area there

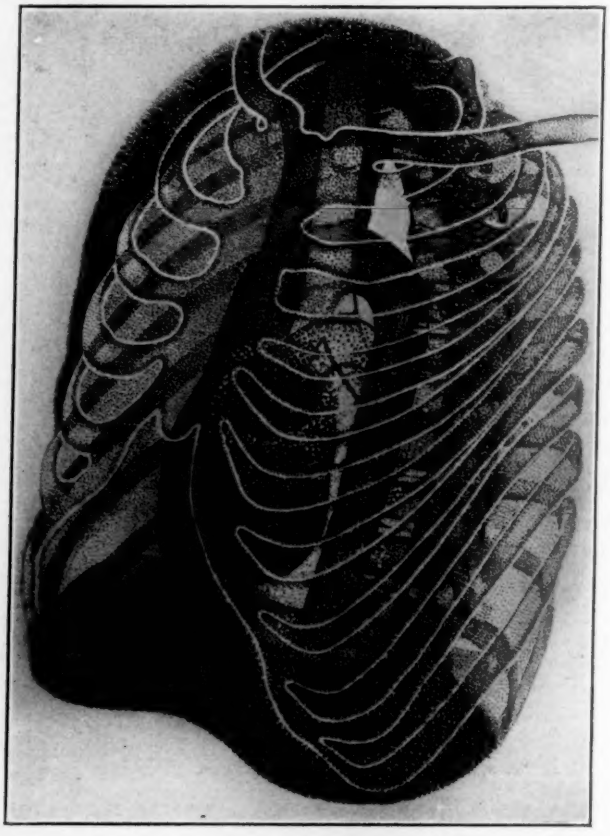

Fig. 2.—Special drawing of normal teleoroentgenogram in the left oblique radioscopic position to show the heart and course of the great vessels (Parkinson and Bedford).

was a low-pitched systolic murmur. The aortic second sound was accentuated. It was succeeded by a high-pitched diastolic murmur. The diastolic murmur became more pronounced when the stethoscope was moved across the left border of the sternum at the level of the third rib. It could also be heard, but with lessened intensity, along the left sternal border as low as the level of the fourth intercostal space. The blood pressure in the left arm was 104/70, in the right arm 100/62, in the left leg 108/66, and in the right leg 110/62. The radial pulses were equal. The femoral, popliteal and dorsalis pedis pulses were of normal amplitude. Examination of the lungs was negative. Abdominal examination revealed no masses. There was

tenderness to pressure over the left upper quadrant. Pelvic examination revealed a relaxed pelvic floor, a first-degree retroversion of the uterus, and a mucopurulent discharge from the cervix. The extremities were negative. There was no edema. There was neither cyanosis nor petechiae. Neurological examination was negative. No signs of collateral circulation were found.

Laboratory Data.—On admission the urine contained numerous erythrocytes and occasional leucocytes. The hemoglobin was 67 per cent. The erythrocyte count was 3,300,000 and the leucocyte count 13,600, of which 85 per cent were polymorphonuclear cells and 15 per cent lymphocytes. The blood Wassermann reaction was negative.

Fluoroscopic examination of the heart and lungs revealed the following: The lung fields were clear. The heart was within normal limits as to size, shape, and position. The arch of the aorta was markedly elongated and dilated, extending upward above the sternal angle to the root of the neck. The aortic impression on the barium-filled esophagus was particularly marked. With the patient in the left oblique position the descending portion of the arch of the aorta could be clearly followed into the shadow of the spine, extending down to a point about at the level of the pulmonary artery. At this level the aorta became distinctly narrowed as though it were surrounded by a constricting band (Fig. 2). Distal to this constriction the arch of the aorta could be seen to widen out again. Scalloping of the inferior borders of the ribs (Roesler's sign) was not present.

The electrocardiogram showed normal rhythm, a heart rate of 96, left axis deviation, a diphasic T_3, and a normal fourth lead. In view of the radioscopic examination, normal blood pressure readings in the upper and lower extremities, the absence of signs of collateral circulation, and the presence of an aortic diastolic murmur, a diagnosis of partial coarctation of the aorta, associated with a bicuspid aortic valve, was made.

The patient was observed in the hospital for a period of ten days, during which time there was no appreciable change in the findings. She was discharged against advice Sept. 8, 1937. She was readmitted to the medical service Nov. 8, 1937. Her history during the interval was as follows: Aside from increasing weakness, she felt fairly well until the morning of Sept. 31, when she developed a severe stabbing pain just to the left of the sternum. The pain radiated to the left shoulder and down the left arm. It appeared suddenly and persisted for several hours, after which it abated and remained as a dull pain in the left chest for several days. On the morning of October 7, while lying in bed, she developed another similar attack of pain. The attack persisted until the night of the same day. The next day she still complained of pain in her left chest and left upper quadrant. Since her previous admission she stated that she had had fever but no chills.

Physical examination on this admission revealed fresh petechiae in both conjunctivae. Examination of the eyegrounds revealed flame-shaped hemorrhages in both fundi and slight choking of both discs. There was a marked pallor of the lips and mucous membranes. The cardiac findings were the same as on the previous admission except that a presystolic murmur was present over the apex. Neither the spleen nor the liver was palpable. A skin test with the nucleoprotein fraction of the nonhemolytic streptococcus was negative on Nov. 11, 1937. On this same day more petechiae appeared in the conjunctivae. The spleen was now palpable and markedly tender. A splenic infarct was suspected. The blood culture was positive for nonhemolytic streptococci, showing one hundred colonies per cubic centimeter. This fact that the patient now had obvious bacterial endocarditis strengthened the diagnosis of a bicuspid aortic valve. The urine on this admission showed a specific gravity of 1.012; it contained albumin (graded 1+), and many leucocytes. The hemoglobin was 48 per cent, the erythrocyte count 3,300,000, and the leucocyte count 11,000. The differential leucocyte count showed 87 per cent polymorphonuclear cells,

12 per cent lymphocytes, and 1 per cent monocytes. The other laboratory findings were not significantly altered. The radioscopic findings of the heart were essentially the same as those previously noted.

Course of the Disease.—Marked tenderness developed over the splenic area and there was tenderness to pressure over the sternum. The patient was given large doses of sulfanilamide without improvement in her condition. The blood culture remained positive. The temperature was septic in type, ranging up to 102° F., with a pulse rate varying between 90 and 120. On Nov. 21, 1937, râles appeared in the right chest below the scapula. Cyanosis developed and the blood pressure dropped. Dyspnea and respiratory distress increased. The patient expired Nov. 27, 1937.

Fig. 3.—Interior view of the heart, showing the left ventricle and the bicuspid aortic valve. The valve was opened through the left posterior commissure, so that as seen in the photograph, the posterior cusp is to the right, the conjoined cusp to the left. The raphe is indicated by the arrow at *a*.

The pertinent autopsy findings were as follows: There was mild pitting edema of the feet and ankles. Each pleural cavity contained a liter of clear fluid and there were 250 c.c. of a similar fluid in the pericardial sac. The lungs were moderately congested and there was a partial atelectasis of the lower lobes. The spleen weighed 500 gm., presented scattered yellow infarcts and a single suppurative infarct 5 cm. in diameter, and showed, microscopically, subacute splenitis. There was a moderately severe passive congestion of the liver. The kidneys presented scattered contracted infarcts and, microscopically, a minimal embolic glomerulitis.

The heart (including the attached portion of the aortic arch) weighed 330 gm. and was not enlarged. The epicardium and myocardium showed nothing of note. The endocardium of the right atrium, right ventricle, and left atrium was normal. The left ventricular endocardium, except for a group of minute, friable vegetations just below the right posterior commissure, was normal. The pulmonary, tricuspid, and mitral valves were normal. There was a bicuspid aortic valve, the free margins of which were covered with and distorted by large, friable vegetations. The cusps showed no thickening near their attached margins and there was no indentation of the central portion of the combined cusp at the point of its attachment. The left posterior commissure was normal; the right posterior commissure was involved in the infective process but there was no evidence of previous fusion. The position of the right-left commissure was occupied by a low raphe (Fig. 3*a*), the smooth, cordlike free margin of which became bifid as it approached and merged with the cusp. Beneath its cordlike margin the raphe was thin and delicate. The breadth of the posterior cusp at the level of its commissures was 25 mm., and that of the combined cusp was 32 mm.; the raphe was equidistant from its extremities. The aorta, in the sinus behind the posterior cusp and at a point midway between its commissures, presented small mycotic aneurysms. The coronary orifices and coronary vessels were normal.

Fig. 4.—Photograph of heart and aorta showing the point of constriction (*a*) just below the insertion of the obliterated ductus arteriosus.

Of the branches of the aorta the left common carotid and left subclavian were distinctly larger than the innominate. The lumen of the aorta between the sites of origin of the innominate and the left common carotid was diffusely narrowed. At the site of attachment of a cordlike obliterated ductus arteriosus the aorta presented a distinct notching which was most marked on its free border (Fig. 4*a*). The lumen at this point was acutely constricted. The diameters of various points of the aortic arch were as follows: root, 1.7 cm.; between innominate and left common carotid, 1.2 cm.; between left common carotid and left subclavian, 1.5 cm.; site of constriction, 1.2 cm.; 3 cm. distal to constriction, 1.7 cm. The segmental branches of the aorta and the internal mammary arteries were normal.

Microscopic sections of the valve rings and myocardium showed no direct evidence of previous rheumatic infection. The myocardium showed areas of diffuse and focal inflammation characterized by polymorphonuclear exudate, as well as a few areas of scarring. The aortic valve presented the typical appearance of subacute bacterial endocarditis. Longitudinal sections at the site of the raphe of the conjoined aortic cusp showed absence of the normal inversion of the aortic wedge.

DISCUSSION

All grades of stenosis of the isthmus of the aorta may occur, varying from complete obliteration to one which is so slight that it may be overlooked on careful post-mortem examination. In the 200 cases of coarctation analyzed by Abbott[1] there were forty-seven in which the arch of the aorta was completely obliterated, 108 of extreme narrowing in which the diameter at the site of the stenosis did not exceed 6 mm., and forty-five in which the stenosis was of a moderate grade approximating one-third the size of the normal caliber of the aorta. The case reported here falls in the last series, which may be considered as a nonclinical group.

The importance of recognizing cases in this group extends beyond mere academic interest. Hitherto, the diagnosis in this nonclinical group has been made only at necropsy. Death in these cases may occur from spontaneous rupture of the aorta, from bacterial aortitis invading the area of coarctation, or from subacute bacterial endocarditis with vegetations on the bicuspid aortic valve which is so frequently associated with coarctation. From a practical viewpoint nonclinical degrees of coarctation are therefore of definite prognostic significance and attempts should be made to recognize them during life. Inasmuch as the clinical features, such as arterial hypertension and signs of collateral circulation, are absent in these cases, the diagnosis can only be arrived at by direct radioscopic examination of the aortic arch, which is best studied in the left oblique radioscopic position. The observation which called our attention to the existence of some abnormality of the aortic arch was the presence of a systolic pulsation and thrill in the suprasternal notch. These signs were perceptible, as subsequent radioscopic examination showed, because the aortic arch occupied an unusually high position.

The bicuspid aortic valve with two distinct cusps is readily accepted as congenital. However, when the valve presents a conjoined segment with a raphe, supportive evidence is required before it may be accepted as a case of developmental arrest.[1] For this type of case the macroscopic criteria of Osler[3] and the microscopic criteria of Lewis and Grant[4] must be fulfilled. We believe that the bicuspid aortic valve in the case here reported was of congenital origin. In the first place, it was associated with a developmental defect of the aorta. The macroscopic criteria of Osler, except insofar as the infective process prevents their demonstration, were fulfilled. Microscopically, the absence of the normal inversion

of the aortic wedge[4, 5] at the site of the raphe satisfied that portion of the criteria of Lewis and Grant. The choice of longitudinal sections precluded the demonstration of the continuity of the fibers of the aortic media across the raphe. Furthermore, because of the fact that there was no microscopic evidence of previous rheumatic infection[6] and, because the existing inflammatory changes were entirely those which may occur during the course of subacute bacterial endocarditis, an inflammatory origin of the bicuspid condition of the valve may be excluded.

CONCLUSIONS

A case of nonclinical coarctation of the aorta associated with a congenitally bicuspid aortic valve is reported, the recognition of which was made possible by radioscopic examination. Because of the frequent association with other congenital vascular anomalies which are of a serious nature, the recognition of nonclinical coarctation is of considerable prognostic importance.

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NONRHEUMATIC CALCIFIC AORTIC STENOSIS

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SINCE the publication of Christian's[1] paper, in 1931, we have identified calcific aortic stenosis as a distinct clinical entity with characteristic, interesting manifestations. As a result of a number of recent publications, we now recognize the frequency and importance of this disease.[2-7] The clinical diagnosis has been greatly facilitated by a growing acquaintance with its distinctive symptomatology, by broadening of the previously rigid diagnostic criteria of aortic stenosis, and by demonstrating the characteristic roentgenographic appearance of the valves.

Apart from the endeavor to improve the means of making the clinical diagnosis, calcific aortic stenosis still offers many problems of interest. A lively discussion has been engendered by uncertainty as to its etiology and as to the exact pathogenesis of its distinctive manifestations, namely, angina pectoris, disturbances in cardiac conduction, syncope, and sudden death. The purpose of this study was primarily to review the clinical features in a group of autopsy cases of calcific aortic stenosis in which one of us had previously excluded the possibility of a rheumatic etiology.[8] As a corollary we attempted to determine whether it was clinically possible to differentiate the rheumatic from the nonrheumatic cases. As a result of this study we are proposing an explanation, compatible with physiologic, clinical, and anatomic observations, for the occurrence in this disease of angina pectoris, syncope, electrocardiographic evidences of conduction disturbances, and sudden death.

ETIOLOGY AND PATHOLOGY OF CALCIFIC AORTIC STENOSIS

It has long been known that calcific aortic stenosis may be the result of rheumatic valvular disease. Mönckeberg[9] was clearly aware of this when, in 1904, he segregated a group of cases of calcific aortic stenosis in which he believed that the lesion was due, not to rheumatic fever, but to primary sclerotic and calcific degeneration. Since that time it has been erroneously assumed that Mönckeberg and others who think that there is a primary degenerative form of calcific aortic stenosis believe that the disease is noninflammatory in all cases. The reports of Christian,[1] Clawson and his co-workers,[10] and others, as well as our own observations, indicate clearly that rheumatic fever is the cause in the majority, perhaps in the preponderant majority, of

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cases of calcific aortic stenosis. There is a dispute only as to whether, in addition to the rheumatic cases, there is also a nonrheumatic, primarily degenerative, calcific aortic stenosis. While various statistical studies of the etiology of this disease point out the importance of rheumatic fever, they do not preclude the possibility of a primary degenerative process in some cases. Detailed histopathologic investigation offers direct evidence that in certain cases the lesion is due to primary sclerocalcific disease and that this lesion can be distinguished microscopically from those caused by rheumatic fever.[8]

In a recent comprehensive review of calcific aortic valvular disease, Clawson and his co-workers[10] concluded that it was invariably due to rheumatic infection. Their conclusion was based essentially on the following observations: (1) A rheumatic history, adherent pericardium, and Aschoff bodies were found almost as frequently in association with calcified aortic stenosis as with other old valvular lesions which were known to be caused by rheumatic fever; (2) macroscopic study of the aortic valves did not indicate that there is a distinctive form of primary sclerocalcific disease; (3) microscopic examination of these valves revealed what was apparently an inflammatory reaction, and the presence of blood vessels, in a high percentage of cases.

As already stated, this evidence merely indicates that rheumatic fever is a frequent cause of calcific aortic stenosis but it does not preclude the existence of a nonrheumatic form of this ailment. Clawson, et al.,[10] point out that a history of rheumatic fever was obtained in 35 per cent of the cases of calcified aortic nodular sclerosis, as compared with 41 per cent in cases in which there were other healed (probably rheumatic) valvular lesions, from which he concluded that the lesions in both groups were of rheumatic origin. Since in the great majority of cases of calcific aortic stenosis the etiology is admittedly rheumatic, the presence of a relatively small group of nonrheumatic cases would have but little effect in diminishing the percentage of positive rheumatic histories for the entire calcific group. Thus, a 6 per cent difference between the incidence of positive rheumatic histories in the more definitely rheumatic (healed) valvular group and the incidence of positive rheumatic histories in the group of 200 cases of calcific aortic stenosis might represent as many as 30 nonrheumatic cases.

Clawson, et al.,[10] stressed the fact that the age at death of individuals with aortic valvular disease did not differ essentially from that of individuals with definitely rheumatic (healed) valvular defects. This similarity would be significant if the age at death of individuals with definitely rheumatic valvular defects was compared with that of individuals who had calcific aortic stenosis without associated disease of the mitral valve. For, since mitral valvular disease is usually due to rheumatic fever, nonrheumatic calcific aortic stenosis is most likely

to be found in individuals without mitral lesions. But an analysis of the data in the report of Clawson, et al., reveals that whereas 54 per cent of the individuals in whom calcific aortic disease was associated with mitral lesions (i.e., an essentially rheumatic group) died before the age of 50 years, only 27 per cent of those with pure calcific aortic disease (sometimes nonrheumatic) died before that age. If we were to exclude some of the very young patients, who were undoubtedly rheumatic, from this pure aortic group, the disparity in age at death between those with nonrheumatic and those with rheumatic calcific aortic valvular disease would be even greater. If the viewpoint of Clawson, et al., that rheumatic fever is the only cause of calcific aortic stenosis were correct, the average age at death of individuals with rheumatic stenosis, as found by these authors, would be much higher than that of individuals with any other rheumatic valvular lesion, a conclusion which is incompatible with the numerous studies of the prognosis of rheumatic heart disease.

The data on sex presented by Clawson and his co-workers[10] also appear to affirm rather than negate the existence of a nonrheumatic type of calcific aortic valvular disease. In their 200 cases there were 165 males and 35 females, a proportion similar to that reported by other observers. This plurality of males is quite disproportionate to the distribution of sex in patients with definitely rheumatic valvular defects.

According to the data of Clawson, et al., there were 111 instances of pure calcific aortic stenosis without mitral lesions. If the aortic defect in all of these cases were due to rheumatic fever, calcific aortic stenosis would be the commonest rheumatic valvular lesion. But this assumption contradicts numerous observations indicating that rheumatic fever attacks the mitral valve most frequently.

In the same series, the location of the calcified nodules in the aortic cusps also sheds light on the etiology of the disease. In rheumatic calcific aortic disease the calcific nodules occur first and predominantly on the ventricular surface of the valve, while in the nonrheumatic degenerative cases they occur on the aortic surface. When the calcification is advanced and widespread, both surfaces may be affected. Clawson, et al., report that in 11 per cent of 106 cases there were calcified nodules on the aortic surface only. This 11 per cent appears to us to represent the minimum percentage of definite nonrheumatic cases of calcific aortic disease, but, in addition, there must have been other nonrheumatic cases in which the calcification had spread to both surfaces of the valve.

An objection is sometimes raised to the possibility of a nonrheumatic calcific aortic stenosis on the ground that the aorta is not as calcified as the aortic valve, but this objection is no more valid than to doubt the primary degenerative nature of calcification and sclerosis

of the aorta in cases in which there is no corresponding calcific sclerosis of the aortic valve. It must be admitted merely that it is not completely understood why excessive amounts of lime are deposited in one site rather than in another. In some instances, the absence of arteriosclerosis at the base of the aorta is due most probably to the protective effect of the stenosis of the aortic orifice.

The histologic studies of Mönckeberg,[9] Geerling,[11] and Giese[12] have already indicated certain characteristic pathologic features of primary calcific aortic stenosis which distinguish this lesion from that secondary to rheumatic endocarditis. Briefly, the following features were observed: (1) Calcification began and was most extensive in the sinus pocket and base of the valve, and progressed thence to the free margin. In rheumatic valves, the calcification began and was most extensive in the distal third of the valve. (2) The calcific process affected predominantly the fibrous layer of the valve cusp on the aortic side of the leaflet. Calcification in rheumatic valves occurred predominantly in the spongiosa and ventricularis layers on the ventricular aspect of the aortic cusp.

More recently, Sohval and Gross[8] not only confirmed these distinctions, but were able to eliminate definitely the possibility of rheumatic infection in a group of cases in which they concluded that the lesion was primary calcific sclerosis of the aortic valves. As a result of extensive studies in the pathology of rheumatic fever, Gross and his co-workers[13] were able to demonstrate that even in cases of old, healed, rheumatic valvulitis, definite stigmas of rheumatic infection could be found in a variety of strategic sites, such as the left auricle, the valve rings, the valve cusps, the pericardium, etc. Thus, in nineteen instances of gross, polyvalvular, healed, rheumatic disease studied by Sohval and Gross[8] there was a very high incidence of widespread, microscopic, rheumatic lesions. Similarly, in thirteen other hearts, in which gross examination showed a healed rheumatic deformity of a single valve, histologic examination revealed a high incidence of rheumatic lesions not only in the grossly affected valve but also in the numerous other cardiac sites in which rheumatic lesions are usually found. It appeared from these histologic studies that pure monovalvular rheumatic disease was probably a rarity. On the other hand, in fifteen hearts with calcific aortic stenosis which resembled microscopically and macroscopically the primary degenerative lesion described by Mönckeberg,[9] detailed microscopic study of the various cardiac sites failed to reveal the lesions found in the rheumatic hearts. As a result of these studies, Sohval and Gross believed that they had definitely demonstrated that nonrheumatic calcific aortic stenosis exists, and had indicated how this form could be differentiated histopathologically from rheumatic aortic disease with superimposed calcification.

TABLE I

NO.	AGE	SEX	ANGINA PECTORIS	CONDUCTION DEFECT	SUDDEN DEATH	SYSTOLIC MURMUR	DIASTOLIC MURMUR	THRILL	B.P.	CORONARY NARROWING	MYOCARDIAL INFARCT	HEART WEIGHT
Patients with failure:												
1.	46	M	+	Arb. block	-	+ Apex and base	+	-	100/80	+++	-	-
2.	77	F	+	-	-	+ Apex	-	-	145/70	+++ Old occlusion	aneurysm	510 gm.
3.	72	F	+	-	-	+ Apex and base	+	-	99/61	ACO Old occlusion	-	550
4.	68	F	-	LBBB	+	+ Generalized	-	-	130/72	+++	-	-
5.	62	M	+	PR = .24 LBBB	-	+ Apex and base Musical	-	+	-	+++	-	-
6.	61	M	+	-	-	+ Apex and base Rough	+	-	130/70	-	-	470
Patients without failure (or circulatory symptoms):												
7.	43	F	-	-	-	-	-	-	104/60	-	-	460
8.	60	F	-	-	-	-	-	-	-	-	-	350
9.	64	F	-	-	-	-	-	-	-	-	-	-
10.	74	M	+	-	-	+ Apex and base	-	-	160/90	++ LAD	-	-
11.	48	M	-	-	-	-	-	-	120/80	-	-	325
Patients with failure and syphilitic aortitis:												
12.	48	M	+	-	+	+ Apex and base Rough	+	-	134/35	+++	-	-
13.	50	M	-	-	-	+ Apex and base	+	-	190/72	++++	+	710
14.	66	M	+	-	+	+ Apex and base	+	-	130/60	+++	-	700
15.	30	M	+	Arb. block	+	+ Generalized	+	+	300/38	-	+	1300

Arb. block = intraventricular conduction defect.
LBBB = left bundle branch block.
PR = PR interval.
ACO = acute coronary occlusion.
LAD = left anterior descending coronary.

CLINICAL FEATURES

This report presents the clinical features in the fifteen examples of calcific aortic stenosis studied histologically by Sohval and Gross.[8] In eleven of the cases there was pure calcific aortic stenosis, without associated syphilitic, rheumatic, or other infectious lesions of the heart and valves. In four cases there was a concomitant syphilitic aortitis and aortic insufficiency. The essential data in all of the cases will be found in Table I. Seven representative cases are presented below.

The clinical manifestations in these nonrheumatic cases did not differ essentially from those in cases of calcific aortic stenosis which have been described by several observers who did not attempt to segregate the rheumatic from the nonrheumatic cases. The fifteen cases studied fell into three groups. In the first group, consisting of six cases (of which Cases 1 to 5, inclusive, are presented in detail), the patients were admitted to the hospital because of symptoms of cardiac failure. In the second group, consisting of five cases (of which Case 11 is presented as an example), the existence of the valvular lesion was not suspected and there were neither cardiac failure nor other symptoms usually associated with the disease, although in one case the possibility of a congenital cardiac lesion was considered because of the presence of an unusual murmur. In the third group, consisting of four cases (illustrated by Case 15), cardiac failure was as predominant a feature as in the first group, but these cases were segregated because of coexisting syphilitic aortic valvular disease.

The characteristic features of calcific aortic stenosis were usually found in the group of patients who were hospitalized because of cardiac failure. These features included dizziness or syncope, angina pectoris, disturbances in cardiac conduction, and sudden death. The hearts in this group presented the severest degree of aortic stenosis and had suffered the greatest strain. In consequence, these hearts had undergone conspicuous hypertrophy and weighed more than those in the other groups.

The incidence of the above-mentioned symptoms is probably higher than would appear from the case reports. Instances of sudden death from calcific aortic stenosis are more likely to appear in coroners' statistics than in the hospital records of individuals admitted because of symptoms of cardiac failure. Certain symptoms of the disease are not likely to be mentioned by a patient who is concerned with the more distressing evidences of cardiac failure. Thus, mention of dizziness, syncope, and angina pectoris is elicited only by specific questioning. Since in most of the cases here reported the presence of calcific aortic stenosis was not suspected ante mortem, specific inquiry as to the occurrence of dizziness and syncope was probably not made. These symptoms will be discussed in detail following the case reports.

Symptoms of cardiac failure may be the first subjective manifestations of the disease. Cardiac failure was the commonest cause of death. The symptoms appeared in an almost uniform sequence. First, there were evidences of left-sided heart failure. Exertional dyspnea was usually the earliest symptom. This was often present for many years before any other symptoms developed. Later, the patients suffered attacks of paroxysmal dyspnea, which usually occurred at night. Eventually, signs of right-sided heart failure appeared, such as peripheral edema, enlargement of the liver, and other evidences of venous engorgement. The duration of life after the onset of right-sided heart failure was brief, rarely exceeding six months.

CASE REPORTS

CASE 1.—F. M., 60-68, a salesman, aged 46 years, entered the hospital because he had had shortness of breath for two weeks. He had never had rheumatic fever. For many years he had experienced pain in the left scapula. For three years he had had attacks of dyspnea on exertion, with asthmatic symptoms, which were ascribed to a neurosis. Three years before admission he suddenly became dizzy, weak, and nauseated. The symptoms subsided after two hours. Eight months later he suffered a similar attack, in which "everything went black for a few hours." Two weeks before admission he had another attack, characterized by sharp epigastric and chest pain, severe dyspnea, and swelling of the ankles.

Examination revealed diffuse râles throughout both lungs and a small area of consolidation at the base of the right lung. The heart was enlarged toward the left. There were a systolic and a diastolic murmur at the apex of the heart, a systolic murmur over the aortic area, and a diastolic murmur in the third left intercostal space. The liver was enlarged; its lower edge was felt 8 cm. below the costal margin. There was slight edema of the ankles. The blood pressure was 100/80. An electrocardiogram showed low voltage in all leads, and thickening and widening of the QRS complexes indicating arborization block. A roentgenogram of the chest showed marked hypertrophy and dilatation of the left ventricle, and moderate enlargement of the right side of the heart. There was diffuse congestion in the lungs.

The *clinical diagnosis* was coronary artery disease with congestion of the lungs. Despite bed rest and digitalization, the patient developed increasing edema of the feet and over the sacrum. He complained of severe precordial, abdominal, and left scapular pain. After five days he began to expectorate bloody sputum. He died nine days after admission.

Post-mortem examination revealed generalized arteriosclerosis; calcific aortic stenosis and insufficiency; cardiac hypertrophy and dilatation; chronic passive congestion of the lungs, liver, spleen, and kidneys; ascites; pulmonary emboli, and infarction of the right lung.

The heart weighed 500 gm. The arch of the aorta was slightly dilated and had lost its elasticity. The right coronary orifice was narrowed. Both coronary arteries showed thickening of the wall, loss of elasticity, and irregular calcified atheromatous plaques.

CASE 2.—E. B., 301521, a woman, 77 years of age, was admitted to the hospital because for one year she had experienced progressive dyspnea, palpitation, and cardiac pain. The pain radiated from the precordium to the left shoulder and arm. In the preceding month she had become orthopneic and had noted edema of the legs.

Examination revealed an acutely ill woman, who was dyspneic, orthopneic, and cyanotic. There were signs of fluid at the base of the left lung. The heart was markedly enlarged to the left and right. There was a soft blowing systolic murmur over the apex of the heart. The pulse was rapid, thready, and barely perceptible. The liver was enlarged and tender. The lower extremities were very edematous. The blood pressure was 145/70.

The *clinical diagnosis* was coronary artery disease and myocardial insufficiency. The electrocardiographic changes (left axis deviation and displacement of the RT segments in Leads I and III) were regarded as compatible with hypertension and myocardial involvement. The patient improved after rest in bed and treatment with morphine and digitalis. Four days after admission she died in an attack of pulmonary edema.

Post-mortem examination revealed generalized arteriosclerosis; calcified aortic stenosis and insufficiency; chronic passive congestion of the liver, spleen, and kidneys; and renal arteriosclerosis.

The heart weighed 510 gm., both ventricles being hypertrophied and dilated. The right coronary orifice was reduced to pin-point size by atheroma. The left anterior descending branch was almost completely calcified; there was an old closure of the vessel near the apex. In the myocardium near the apex there was an old fibrotic area whose endocardial surface was covered by a thrombus. The myocardium was studded with yellow flecks. The aorta was inelastic and showed severe arteriosclerosis.

CASE 3.—C. W., 312969, a woman, aged 72 years, who was known to have had a cardiac murmur for thirty-five years, had long complained of palpitation and dyspnea on exertion but had always been able to do strenuous work. For fifteen years she had experienced precordial pain and epigastric distress. In the preceding two years her dyspnea had increased greatly, and orthopnea and edema of the ankles had appeared. For the preceding three weeks these symptoms had become intensified, and she had developed severe precordial oppression and a hacking cough.

Examination revealed signs of left- and right-sided heart failure, including hydrothorax and ascites. The heart sounds were of poor quality. There was a soft systolic murmur at the apex and the base. At the left of the sternum there was a diastolic murmur which later disappeared. The patient's blood pressure varied between 110/70 and 88/52. An electrocardiogram revealed left axis deviation and a negative T in Lead I. The urine contained a large amount of albumin and many red and white blood cells.

The *clinical diagnosis* on admission was coronary artery disease, rheumatic mitral stenosis, aortic insufficiency, and myocardial failure. The patient's condition grew progressively worse. Her blood urea nitrogen mounted to 90 mg. per 100 c.c. and she died three weeks after admission.

Post-mortem examination revealed extreme calcific aortic stenosis; calcification of the mitral ring; generalized cardiac hypertrophy and dilatation; pulmonary infarction of recent origin; necrotizing cystitis; chronic passive congestion of the viscera.

The heart weighed 550 gm. The aorta was smooth. The left anterior descending artery was entirely occluded by a fresh thrombus. The left coronary artery and the right posterior descending coronary artery were calcified and narrowed, and each showed evidence of an old occlusion. There was extensive myomalacia and endocardial thrombosis of the left ventricle.

CASE 4.—I. R., 335867, a woman, aged 68 years, had a twenty-five-year history of asthma and chronic bronchitis. Four years before admission she had had a cerebral thrombosis with resultant hemiplegia. Five days after catching a cold she went to bed because of weakness, dyspnea, and orthopnea.

Examination revealed an acutely ill, dyspneic, orthopneic, and cyanotic woman. There were diffuse râles throughout the lungs. There was a harsh systolic murmur all over the precordium, most intense at the base. The blood pressure was 138/70, and later 122/74. The total leucocyte count was 18,000, of which 90 per cent were polymorphonuclear leucocytes. An electrocardiogram revealed left bundle branch block.

The *clinical diagnosis* was bronchopneumonia, chronic bronchitis, emphysema, and cardiac failure. The patient ran a febrile course and died four days after admission.

Post-mortem examination revealed calcific aortic stenosis and calcification of the mitral ring; diffuse bronchopneumonia, chronic bronchitis and emphysema; cylindrical bronchiectasis; nephrocirrhosis atherosclerotica lenta progressa; chronic passive congestion of the viscera; subacute splenic swelling.

The heart weighed 550 gm. The coronary arteries and their branches showed marked atherosclerosis and narrowing. The aorta revealed severe atherosclerosis and dilatation of its arch.

CASE 5.—L. S., 346315, a laborer, aged 62 years, had suffered weakness, precordial pain, substernal oppression, dyspnea, and orthopnea for one and a half years. For six months he had been confined to bed because of swelling of the legs and abdomen. He had had nosebleeds frequently, and bloody stools for four weeks. On the day of admission he had coughed up bloodtinged sputum.

Examination revealed an emaciated old man who was somewhat dyspneic and cyanotic. The heart was enlarged. There were a systolic thrill and a harsh systolic murmur in the aortic area. At the lower end of the sternum and at the apex there was a musical systolic murmur. There was extreme edema of the lower extremities and over the sacrum. There was free fluid in the abdominal cavity. The blood pressure was 94/54. A roentgenogram of the chest showed hypertrophy and dilatation of the left ventricle. An electrocardiogram revealed left bundle branch block. The PR interval measured 0.24 second.

The *clinical diagnosis* was cirrhosis of the liver, coronary artery disease, and atherosclerotic calcification of the aortic valve. Despite abdominal paracenteses and treatment with mercurial diuretics, the patient became progressively worse and died eight days after admission.

Post-mortem examination revealed calcific aortic stenosis; primary carcinoma of the liver with extension into the portal vein and inferior vena cava; cirrhosis of the liver.

The heart weighed 460 gm. There were moderate sclerosis and narrowing of the coronary arteries.

CASE 11.—I. W., 373542, a tailor, aged 48 years, had had hematuria, frequency of urination, and nocturia for two years, during which time he had lost 18 pounds. There was no history of rheumatic fever or cardiac disease.

Examination revealed a chronically ill, emaciated man. His heart was somewhat enlarged. There was a loud, blowing, systolic murmur over the entire precordium, radiating to the back. On rectal examination, an egg-sized mass was felt just above the prostate. The blood pressure was 120/80.

The *clinical diagnosis* was neoplasm of the bladder, congenital heart disease, and pulmonary emphysema. Cystoscopy disclosed a papillary neoplasm involving the trigone. An electrocardiogram showed slurring of the QRS complexes. Partial resection of the bladder was performed, several remaining papillomatous tumors were electrocoagulated, and the right ureter was reimplanted. Osteomyelitis of the pubis and a suprapubic sinus developed, after which the patient ran a febrile course for many months and finally succumbed.

Post-mortem examination revealed a necrotizing cystitis; bilateral ureteral calculi and ascending ureteropyelonephritis; calcific aortic stenosis; hypertrophy of both ventricles.

The heart weighed only 325 gm. despite the apparent hypertrophy of the ventricles. The coronary ostia were normally patent. The coronary vessels were slightly thickened, but there was no diminution in the caliber of their lumina.

CASE 15.—M. S., 331428, was a man, aged 30 years, whose father had died of aortitis and whose mother had had an aortic aneurysm. Three years before admission he had had ulceration of both eyes. At that time his blood gave a positive Wassermann reaction. Thereafter he had suffered increasing weakness, dyspnea on exertion, and attacks of angina pectoris. For one month he had had insomnia, orthopnea, edema of the ankles, and a productive cough.

Examination revealed bilateral corneal opacities, signs of fluid in the right pleural cavity, and extreme enlargement of the heart. There was a systolic thrill over the aortic area and at the apex of the heart. A systolic and a diastolic murmur were heard all over the precordium. There was a Corrigan pulse. The liver was enlarged and tender. There was slight peripheral edema. The blood pressure was 300/38.

The *clinical diagnosis* was congenital syphilitic aortitis with aortic insufficiency, questionable stenosis or calcification of the aortic ring, and myocardial insufficiency. A roentgenogram of the chest showed enormous enlargement of the left and right ventricles, and pleural effusion at the base of the right lung. An electrocardiogram revealed a high-grade intraventricular conduction defect. Both the blood Wassermann and Kahn reactions were positive (2 plus). The pulse became completely irregular and there was a pulse deficit. Five days after admission, while apparently comfortable, and engaged in conversation, the patient suddenly developed profuse diaphoresis, became markedly cyanotic, and died.

Post-mortem examination revealed syphilitic aortitis and aortic insufficiency; calcific aortic stenosis with an acquired bicuspid condition of the valve; young and old myomalacia of both ventricles; chronic passive congestion of the liver, spleen, kidneys, intestines, and lungs.

The heart was enormous, weighing 1300 gm. The mouth of the right coronary artery was narrowed. The left and right coronary arteries and their branches were sclerotic, but not narrowed. Despite the absence of coronary occlusion, there was an area of softening of recent origin in the anterior wall of the left ventricle near the apex. There were also diffuse areas of myofibrosis throughout both ventricles.

DISCUSSION

The following discussion is limited to a consideration of the occurrence and pathogenesis of certain characteristic symptoms of calcific aortic stenosis, and the diagnosis and differential diagnosis of the disease.

Angina Pectoris.—Angina pectoris has been reported as occurring in 20 to 25 per cent of the cases of calcific aortic stenosis. Cardiac pain, with or without the typical radiation of angina pectoris, and usually due to effort, occurred in nine of our fifteen cases.

The pathogenesis of angina pectoris in this disease has been the subject of considerable discussion but is still obscure. Because of the frequency of a diastolic murmur in association with aortic stenosis, the cardiac pain has been attributed to concomitant aortic insufficiency. Several objections may be raised to this theory. Despite the diastolic murmur, there is no dynamically significant insufficiency; the typical

peripheral circulatory phenomena of free aortic regurgitation are absent unless syphilitic aortic insufficiency is present also. Furthermore, angina pectoris has been observed in cases of calcific aortic stenosis in which there was neither a diastolic murmur nor any other clinical evidence of aortic insufficiency. Three such examples were encountered in our series. Finally, there is some question whether the pain in aortic insufficiency (usually in syphilitic aortic insufficiency) is due to the valvular lesion itself. More probably, the pain results from the narrowing of the coronary ostia which so often occurs in syphilitic aortitis. In cases of rheumatic aortic insufficiency angina pectoris is much more infrequent; it is not typical in that it usually occurs without effort and is associated with vasomotor phenomena. The active myocarditis and the extremely low diastolic pressure frequently found in such cases may account in part for the anginal pain.

More logical theories have attributed the pain in calcific aortic stenosis to myocardial ischemia, but as yet there has been neither anatomic confirmation of the existence of such ischemia nor a clear physiologic explanation for its development. Many observers have been unable to find any narrowing of the coronary arteries, such as might be expected to produce myocardial ischemia. In fact, they have emphasized that these vessels show surprisingly little sclerosis, and that their lumina may even be widened. Boas[4] found the coronary arteries normal at necropsy in two individuals who had suffered from angina pectoris; in one, death had occurred following an attack which closely resembled acute coronary thrombosis. He concluded that the pain was due to myocardial ischemia caused by an obstruction at the aortic rather than at the coronary orifice, and that associated cardiac failure contributed to the development of the symptoms. This explanation appears obscure since normal aortic pressure is usually maintained even when there is extreme stenosis of the aortic valve. Recently, Contratto and Levine[7] attributed the angina pectoris to myocardial ischemia caused by suction of blood from the coronary arteries by acceleration of the blood flow past the orifices of these vessels. These authors also quoted the views of Harrison, who suggested that the cardiac pain is due to two factors: (1) the augmented cardiac work, resulting from the elevated intraventricular systolic pressure and from the extremely rapid ejection velocity; and (2) coronary vasoconstriction. The first factor is undoubtedly important, but the second is purely hypothetical.

Our studies offer pathologic and clinical support for the theory that myocardial ischemia is the cause of angina pectoris in calcific aortic stenosis. In some instances we have found severe narrowing of the coronary vessels or their lumina, with or without coronary occlusion and myocardial infarction; in others we have seen acute myocardial damage without recent coronary occlusion. Although in calcific aortic

stenosis the coronary vessels are usually surprisingly smooth, they were significantly narrowed in three of the six nonsyphilitic cases in which angina pectoris was present. In addition, the coronary ostia in these cases were narrowed by calcific plaques in the sinus pockets; in two of the cases there was an old occlusion of a major coronary branch. More significant are the two cases of angina pectoris in which there was evidence of myomalacia of recent origin without coronary occlusion. These cases are important because they are examples of myocardial ischemia, of a degree sufficient to produce acute anatomic alterations, resulting from functional coronary insufficiency. Since these studies, we have observed other instances of aortic stenosis in which there was acute myomalacia without recent coronary occlusion. In view of these evidences of extreme myocardial ischemia due to functional coronary insufficiency, it is reasonable to suppose that similar, though less intense, myocardial ischemia may account for those instances of angina pectoris in which there is no anatomic change either in the heart muscle or in the coronary vessels.

A physiologic explanation of, and support for the existence of, functional coronary insufficiency in cases of aortic stenosis is found in the recent studies of Green.[14] He demonstrated, first, that in cases of aortic stenosis there was a significant reduction in the minute-volume flow through the coronary arteries and, second, that this flow could not easily be increased when there was an enhanced myocardial demand for blood. Despite extreme aortic stenosis, an essentially normal aortic pressure is maintained by the abnormally strong left ventricular contraction that is associated with the tremendous elevation of intraventricular pressure, but, at the same time, the elevated intraventricular pressure diminishes the systolic flow (and minute-volume flow) of blood through the coronaries by compressing the peripheral coronary vessels and thus increasing the coronary resistance during systole. The mechanism is similar to that involved in the blanching of a tightly clenched fist. Thus, there may be an inadequate coronary flow even at rest. Usually, however, this inadequacy becomes significant only during exertion, when an increased coronary flow is needed. Because of the already extremely high intraventricular pressure, the left ventricle finds it difficult, or impossible, to augment further the force of its contraction and the aortic pressure. As a result, there may be, during exertion, an inadequate coronary flow with consequent myocardial ischemia. As long as the heart weight is normal there may be little or no myocardial ischemia, but when the heart is noticeably hypertrophied the ischemia due to a relatively insufficient coronary flow may become intense. This explanation is supported by the fact that, in our series, in those cases in which angina pectoris did not occur the hearts were normal or only slightly hypertrophied, while in those cases in which it did occur the heart weights usually exceeded 500 gm.

The theory that myocardial ischemia is the cause of angina pectoris in cases of calcific aortic stenosis is further supported by the electrocardiographic changes. There is usually left axis deviation, which may, of course, be due to the hypertrophy of the left ventricle. More significant are those changes in the T-wave and RST segments which are frequently encountered in this disease. Because of these changes the electrocardiogram is often interpreted as indicating myocardial disease, and a clinical impression of coronary artery disease is apparently verified. When electrocardiograms are taken repeatedly, the progressive alterations in the T-waves and RST transitions are sometimes interpreted as indicating coronary thrombosis, an interpretation which the clinical picture seems to confirm. These electrocardiographic abnormalities are explicable if we accept the hypothesis that with extreme calcific aortic stenosis there is actually myocardial ischemia similar to that associated with coronary arteriosclerosis or occlusion.

Conduction Disturbances.—Complete heart block, bundle branch block, intraventricular conduction defects, and delayed auriculoventricular conduction occur with sufficient frequency in calcific aortic stenosis to be considered characteristic of the disease.[4, 15] In the electrocardiograms of the patients in the present series, left bundle branch block was observed three times, intraventricular conduction disturbance (arborization block) twice, and a prolonged PR interval twice. These abnormalities occurred in four of the fifteen cases.

These disturbances in conduction, especially complete heart block, have been attributed to organic disease of the bundle of His, caused by an extension of the calcific process from the aortic valve to the fibrous septum.[15] While we, as well as others,[16] have occasionally observed such calcific destruction of the bundle, we have seen heart block in some cases in which such organic changes could not be demonstrated. Lime salts were not found in the microscopic sections containing the bundle in any of our four cases in which there were conduction disturbances. While this is inconclusive without detailed study of serial sections, there are other reasons for believing that the conduction disturbances are not invariably, nor even usually, due to organic calcific interference with conduction. First, it would be difficult to explain the intraventricular conduction defects, for the calcific process does not extend beyond the main bundle or the beginning of its main branches. Second, the type and degree of conduction disturbance in a given case are often variable and transient. Thus, in one case of calcific aortic stenosis which we have observed (not included in this series), the electrocardiogram first revealed only left axis deviation and a negative T-wave in Lead I. A week later the PR interval was prolonged to 0.28 second. Shortly afterward there was a transient complete heart block and, eventually, an intraventricular conduction disturbance. In Case 4 of Boas'[4] report, heart

block was likewise transient and occurred only on exertion, simultaneously with angina pectoris. It is difficult to correlate these observations with the conception of a fixed organic calcific lesion in the bundle or its branches. On the other hand, they are clearly compatible with our belief that the disturbances in conduction, like angina pectoris, are due to myocardial ischemia. This does not preclude the fact that in some instances of conduction disturbance calcific deposits in the bundle play a contributory or dominant role.

Dizziness and Syncope.—Gallavardin[17] has stressed the frequency of dizziness and syncope in cases of calcific aortic stenosis. He believes that these symptoms are due to sudden, transient, cerebral anemia, caused by an insufficient aortic output. He bases this belief on electrocardiograms made during syncope of effort, which showed that the heart did not stop contracting while the pulse beat entirely disappeared. Marvin and Sullivan[6] suggested that syncope, like sudden death in this disease, is due to a hyperactive carotid sinus reflex.

There are two significant observations as to the occurrence of dizziness and syncope which are pertinent to their pathogenesis. In the first place, these symptoms tend to occur in individuals who suffer from angina pectoris and, second, they tend to occur during effort. This suggests a similarity between the mechanism which produces angina pectoris and that which causes dizziness and syncope. Dizziness and syncope, like angina pectoris, occur in those individuals in whom there is extreme narrowing of the aortic orifice, and a consequent marked compensatory hypertrophy of the left ventricle. Under ordinary circumstances the increased intraventricular tension is sufficient to maintain a normal aortic, and consequently a normal cerebral, arterial pressure despite the valvular stenosis. But there is no reserve for further elevation in intraventricular pressure when exertion requires an increase in the cerebral vascular flow. Thus dizziness and syncope result from the cerebral anemia that is caused by a relative cerebral arterial insufficiency.

Sudden Death.—The frequency of sudden death in cases of calcific aortic stenosis has been noted by many authors, but its pathogenesis remains obscure. It occurred in three of our cases. Those individuals who die suddenly of aortic stenosis have usually suffered from angina pectoris, dizziness or syncope, or disturbances in cardiac conduction. The pathogenesis of sudden death would, therefore, seem to be similar to, or identical with, that of the above-mentioned manifestations. The commonest of the natural causes of sudden death is myocardial infarction due to coronary artery occlusion. As we have seen, myocardial infarction may occur in calcific aortic stenosis, due either to associated coronary thrombosis or to extreme coronary insufficiency. In some instances of severe myocardial ischemia death may occur before an infarct has formed. Whether sudden death may also occur in this

disease as a result of myocardial ischemia insufficient to produce infarction remains uncertain. Such myocardial ischemia may, however, be sufficient to produce a high degree of heart block, with consequent cerebral anemia or cardiac standstill, or it may cause ventricular fibrillation.

Cerebral anemia, as we have seen, may be due directly to an inadequate supply of blood through the cerebral vessels. It may produce merely dizziness or syncope, but occasionally, if extreme, sudden death. Marvin and Sullivan[6] have suggested that a hypersensitive carotid sinus also may produce cardiac standstill and sudden death, but Contratto and Levine[7] were unable to produce dizziness or syncope in nineteen out of twenty-one patients with calcific aortic stenosis by pressing on the carotid sinus. It is possible, however, that when myocardial ischemia has already produced some degree of conduction disturbance, reflexes from a hypersensitive carotid sinus may help to precipitate sudden death. Two cases have been reported in which sudden death may have resulted from the formation of an occluding thrombus over the stenotic aortic valvular orifice.[18]

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

There is no longer any reason why the clinical diagnosis of calcific aortic stenosis should not be made in most instances of the disease. Of course, its recognition is simple when the classical criteria are present, namely, an aortic systolic murmur and thrill, absence of the second aortic sound, a characteristically small delayed pulse, and enlargement of the left ventricle. Calcific aortic stenosis should be suspected, even in the absence of a thrill, if there is a very rough, or musical, systolic murmur and enlargement of the heart in a person past 50 years of age with no evidence of organic mitral disease. Calcification of the valves may then be confirmed by roentgenologic examination, especially by fluoroscopy, as described by Sosman and Wosika.[5]

Most frequently the only physical sign of calcific aortic stenosis is a loud, rough, whistling or musical murmur at the base of the heart, over the sternum, or over the entire precordium. In the absence of hypertension such a murmur should always suggest the possibility of calcific aortic stenosis, especially if there is evidence of left ventricular enlargement or if there is a history of dizziness, syncope, or angina pectoris, and if there are disturbances of cardiac conduction. The provisional diagnosis may then be verified by a roentgenologic demonstration of calcification of the aortic valve.

In about half of the cases of calcific aortic stenosis there is an associated aortic diastolic murmur suggestive of aortic insufficiency, but none of the dynamic changes of aortic insufficiency are present. If an aortic diastolic murmur is heard in a patient who has a negative Was-

sermann reaction, no history of syphilis, no associated mitral lesion, and none of the peripheral circulatory phenomena of aortic insufficiency, a diagnosis of calcific aortic stenosis should be considered and evidence of calcification of the heart valves sought by fluoroscopy.

Calcific aortic stenosis is most often confused with mitral insufficiency, aortic insufficiency, and arteriosclerotic heart disease (coronary artery disease). Mitral insufficiency is considered when, as happens frequently, there is only a systolic murmur. Aortic insufficiency is diagnosed because of the frequent presence of a diastolic murmur at the base of the heart along the sternum. The differentiation of calcific aortic stenosis from these lesions has already been discussed.

The differentiation of calcific aortic stenosis from coronary artery disease may be extremely difficult because, as we have seen, the symptoms of both are due essentially to myocardial ischemia. Angina pectoris, disturbances in conduction, abnormalities of the T-waves, cardiac failure, and sudden death are caused by both of these conditions. Attacks of dizziness and syncope, when present, favor a diagnosis of calcific aortic stenosis, rather than arteriosclerotic heart disease. If, in addition, there is a distinctive murmur or a systolic thrill, the differentiation from coronary artery disease is clear. Calcific aortic stenosis should be considered as a diagnostic possibility in any patient with cardiac failure of obscure etiology. In all doubtful cases the cardiac valves should be examined in detail fluoroscopically and roentgenographically for evidence of calcification.

The differentiation of rheumatic from nonrheumatic calcific aortic stenosis usually cannot be made from the symptoms and physical signs alone. If there is a history of rheumatic fever, a rheumatic etiology is almost certain. If the patient is below the age of 50, the aortic stenosis is usually due to rheumatic fever. When there is definitely an associated mitral stenosis, the aortic, like the mitral, lesion is almost invariably rheumatic. When the physical signs of mitral stenosis are uncertain, roentgenologic evidence of unusual left auricular or right ventricular enlargement suggests associated rheumatic mitral disease. Similarly, if the electrocardiogram shows right ventricular preponderance, due apparently to mitral disease, the calcific aortic stenosis is probably rheumatic.

SUMMARY

1. A study was made of fifteen cases of calcific aortic stenosis in which detailed pathologic examination (previously reported) had shown that the lesion was nonrheumatic. In four of the cases there was an associated syphilitic aortitis.

2. While in most cases of calcific aortic stenosis there is considerable evidence that the etiology of the lesion is rheumatic, this evidence does not preclude the existence of a nonrheumatic form of the disease.

3. The cases in our series fell into three groups. The first, consisting of six cases, was characterized by the development of left- and right-sided heart failure. The history of these patients revealed the typical symptoms of calcific aortic stenosis, including angina pectoris, dizziness, and syncope. Electrocardiograms frequently showed varying degrees of heart block, such as bundle branch block and intraventricular conduction disturbances, and abnormalities of the T-waves and RST transitions. In occasional cases death occurred suddenly.

In the second group, consisting of five cases, the valvular lesion was discovered accidentally in patients who died of some unrelated disease. Neither the characteristic symptoms of the valvular abnormality nor evidences of heart failure were present.

The third group, containing four cases, resembled the first, both in the occurrence of cardiac failure and in the appearance of the other characteristic symptoms. These cases were segregated because there was associated syphilitic aortitis and aortic valvular disease.

4. Seven cases typifying these three groups were presented in moderate detail.

5. The occurrence and pathogenesis of angina pectoris, conduction disturbances, dizziness and syncope, and sudden death were discussed.

A. Angina pectoris is believed to be caused by myocardial ischemia due to coronary insufficiency. When the patient is at rest, coronary insufficiency is due partly to the increased demand for blood made by a greatly hypertrophied heart, and partly to the diminished coronary flow. The coronary flow is reduced by the increased peripheral coronary resistance resulting from the extremely high systolic pressure within the left ventricle. During exertion the coronary insufficiency becomes more marked. Verification of the existence of coronary insufficiency in these cases is furnished by the occasional instances of myocardial infarction without acute coronary occlusion and by the electrocardiograms, which may resemble those of coronary occlusion.

B. The conduction disturbances, as well as the changes in T-waves and RST transitions, were similarly explained as being caused by myocardial ischemia due to coronary insufficiency. Occasionally, heart block is due to extension of the calcific process to the septum, but the nature of some of the conduction disturbances, their occurrence in some patients on effort, and their transience suggested that they were due predominantly to myocardial ischemia.

C. Dizziness and syncope occur almost always on effort. They are thought to be due to cerebral ischemia. The already high left intraventricular pressure necessary to compensate for extreme aortic stenosis can be further elevated only with difficulty when there is a demand for increased cerebral blood flow. Occasionally, a hypersensitive carotid sinus also may play a role.

D. Sudden death in this disease may have various causes. It may be due to coronary thrombosis, or to myocardial infarction resulting from severe ischemia without acute occlusion (i.e., from coronary insufficiency). Occasionally it may be due to severe cerebral ischemia, obstructing thrombi on the stenotic aortic valve, a hypersensitive carotid sinus reflex, cardiac standstill, or ventricular fibrillation.

6. A summary was given of the means of diagnosing calcific aortic stenosis, of differentiating it from the diseases with which it is ordinarily confused, and of distinguishing the rheumatic from the nonrheumatic cases.

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THE DEVELOPMENT OF THE ELECTROCARDIOGRAM OF THE EMBRYONIC HEART*†

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THE obviously interesting possibilities of electrocardiograms from embryonic hearts have led to many attempts to secure such records. The technical problems involved, however, have proved to be varied and troublesome and the results none too consistent. Physiologists well equipped to deal with the matter of electrical recording have been handicapped by the lack of a detailed knowledge of heart development and by unfamiliarity with satisfactory methods of handling living embryos. Embryologists, to whom a knowledge of cardiac development is a stock in trade, have not been trained to cope with the intricate technique of recording and the difficult matter of interpreting minute electrical changes. With the rapid progress that has been made in electrical recording and in the manipulation of living embryos during recent years, it seemed as if it should be fruitful to attempt a group attack on this problem of the embryonic electrocardiogram, in which the collaborators among themselves would have first-hand knowledge of all the necessary phases of the work.

LITERATURE

As is natural, the earliest work in this field dealt with relatively advanced fetuses which might be expected to furnish records more readily comparable with those from adults. In 1906, Cremer[1] attempted to secure fetal electrocardiograms in the last month of gestation by the use of vaginal-abdominal or recto-abdominal leads on pregnant women. Similar efforts to obtain electrocardiograms from the fetus in utero, using also as variants of Cremer's original method two external abdominal leads, were made by Foà[2] (1911), Haynal and Kellner[3] (1923), Sachs[4] (1923), and Maekawa and Toyoshima[5] (1930). The superimposition of a weaker fetal electrocardiogram on a stronger maternal record and the occurrence of irregularities in the records which did not appear to be attributable to either fetal or maternal heart have made the results obtained from such an approach exceedingly difficult to evaluate with any certainty.

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Greater success has attended efforts to secure electrocardiograms by the use of direct leads from fetuses removed in cases of hysterectomy and kept alive for a time in warm physiologic saline solution. Easby[6] (1934) has reported on the records of a 4½ month fetus thus obtained, and Heard, Burkley and Schaefer[7] (1936) succeeded in making good records from a series of eleven fetuses ranging in age from the tenth to the twenty-fifth week of gestation. These observations clearly indicate that the embryo develops an electrocardiogram similar to that of the adult at a surprisingly early age, and that any efforts to study the manner in which the characteristic adult waves are established must be undertaken on embryos in which the early stages of heart formation are occurring. The almost insurmountable difficulty of securing anything like a complete series of living human embryos in this age range has directed attention toward the embryos of animals adaptable to experimental investigation.

Wertheim-Salomonson[8] (1913) was the first to study the heart action of really young embryos by electrocardiographic methods. Using the chick as an experimental animal he succeeded in taking records from embryos as young as 60 hours. He was greatly handicapped, however, by the lack of amplification methods such as have since become available, and his records of these early stages showed only slow rises and falls with no clear cut phases such as would be anticipated from what is known of the character of the heart action at this stage. Not until the fifth to sixth day did his records show anything like a regular electrocardiographic pattern beginning to be recognizable. Cluzet and Sarvonat[9] (1914) and Spadolini and Giorgio[10] (1921) encountered the same difficulties, their records from young embryos showing nothing sufficiently consistent to warrant any attempt at interpretation.

That electrocardiograms of adult pattern are obtainable much earlier than was indicated by such results was shown by Külbs[11] (1920), who greatly improved the recording technique and obtained tracings from chick embryos showing the emergence of practically all of the adult characteristics as early as the third day of incubation. In agreement with Külbs' results, Robb,[12] in the abstract of her report to the International Physiological Congress (1929), stated that the beginnings of P-waves and of the QRS-T complex were becoming recognizable between fifty and seventy-two hours.

Further progress in the technique of recording was shown in the work of Lauche and Schmitz[13] (1931) and that of Lueg and Höfer[14] (1933). Both these papers, however, dealt with explanted hearts or with cultivated heart fragments. Some of such observations, especially those of Lueg and Höfer, and of Katsunuma and Inada[15] (1933), on isolated atrial and ventricular portions of the heart are exceedingly interesting, but they need to be evaluated in relation to records

of the intact heart acting under more nearly normal conditions. Moreover, the hearts studied by these workers were for the most part rather too old to show the most interesting changes involved in the development of an electrocardiogram of adult configuration.

A description of a carefully worked-out technique for recording electrical changes in the embryonic heart was published by Pollack[16] in 1931. This was followed by a paper in collaboration with Dionne and Schafer[17] (1931) on amplification technique, and a later paper by the same group (Dionne, Schafer, and Pollack,[18] 1932) giving some of the results obtained by these methods. The embryos they used were for the most part older than those on which we are reporting, their series running from the fourth to the twentieth day, but when their observations and ours dealt with comparable material it is interesting to note that the potential changes recorded are quantitatively in close agreement. They observed, however, a wave which they called the "P a" wave, with which we found nothing precisely comparable. This wave appeared immediately following the P-wave and was regarded by them as an auricular phenomenon comparable to the T-wave of the ventricular complex. Among our records from older embryos—not here illustrated—puzzling, complex P-waves were occasionally seen. We were inclined to regard them as conduction irregularities caused perhaps by unsuccessful maintenance of favorable conditions in the preparation, rather than as a normal phenomenon. None of them seemed to us to correspond with the "P a" wave described by Dionne, Schafer, and Pollack, unless the rise following the P-wave in Fig. 7 could be so interpreted.

In a short paper on the influence of digitalis on the embryonic electrocardiogram, Lagen and Sampson[19] (1932) state that multiphasic curves are obtainable from chick embryos as early as the thirty-sixth hour of incubation. Regrettably, no illustrations of their records were included, so that satisfactory comparison of their interesting findings with other available data is not possible.

The most satisfactory electrocardiographic records from young embryonic hearts which we have been able to find in the literature are those of Külbs,[11] referred to previously, and those of Bogue[20] (1933). The records Bogue reproduces are clear-cut and convincing as to the very early appearance of polyphasic tracings. Comparing Bogue's records with those of earlier workers it is apparent that, as amplifying apparatus has improved, the beginnings of the characteristic waves of the adult electrocardiogram have become recognizable in progressively younger embryos. Moreover, it is in these earliest phases of heart development that the most significant changes in the character of its beat are known to occur. For these reasons our own efforts were directed primarily toward securing records from the time the heart beat was just commencing, through the period of rapid

changes in structure and action which occur during loop formation and the establishing of the fundamental regional divisions of the heart.

METHODS

The eggs used were procured locally from white Plymouth Rock hens and artificially incubated by the usual laboratory methods. For taking electrocardiograms, embryos of known incubation ages were removed from the shell to permit concurrent observations of heart action and to facilitate more accurate manipulation. The matter of unhampered manipulation is of particular importance in connection with the precise placing of the microelectrodes, for even slight differences in their position may be of great importance in the interpretation of the records.

The technique of removal and subsequent handling followed in a general way the methods used by Patten and Kramer[21] (1933) for their microcinematographic recording of the early heart beats. Eggs were opened under saline solution kept at 38° C. By means of a circular cut through the blastoderm, well peripheral to the yolk-sac blood vessels, the embryo was freed from the yolk. After removing the vitelline membrane, the embryo was floated into a shallow Stender dish from which a small quadrant of the side wall had been cut. The excess fluid having been pipetted off, the embryo and its essential membranes were spread out on the bottom of the dish in as nearly as possible their normal position. Small strips of filter paper adherent to the nonvascular periphery of the membranes were used to hold the embryo in position. With the cover in place, such a chamber may be freely handled without injury to the contained embryo. If kept at incubation temperatures, the embryo will live in it for many hours and even continue to grow. There was every evidence, certainly throughout the relatively short period necessary for our observations, that the heart was behaving normally.

The small opening referred to as having been cut in the side wall of the Stender dish served both as means of access for introducing fresh saline solution and for the insertion of the microelectrodes. In another series of experiments, to be reported later, this opening served as a means of introducing drugs. It could readily be covered when not actually in use.

For the taking of the electrocardiographic records the chamber with an embryo mounted in it was placed on the stage of a binocular dissecting microscope in connection with which was mounted a Chambers micromanipulator. The microscope and micromanipulator were housed in a specially constructed, copper-shielded incubator which was suspended by springs from the ceiling of the electrocardiographic room. Working through arm holes in the incubator, it was possible, with the aid of the micromanipulator, to place the electrodes accurately at the desired locations on the embryo. When all adjustments had thus been made the arm holes were closed with copper-shielded doors for the period of the actual recording.

Various types of electrodes were tried, with little indication of differences in their performance. The electrode used in most of the experiments consisted of a small ball of platinum formed at the end of a platinum wire. The wire was enclosed in drawn glass tubing fused around the base of the ball to prevent any liquid from creeping up the wires. A pair of such electrodes, matched as closely as possible, were mounted in adjustable brass tubes which permitted their being firmly clamped in the micromanipulator arms. Immediately before use the platinum balls were coated with platinum black. A second type of electrode which also gave good results consisted of capillary glass tubing containing isotonic saline-agar gel in which chloridized silver wires were embedded.

The changing potentials picked up by the electrodes were first passed through a three-stage amplifier and then recorded with a Hindle electrocardiograph. The first and second stages of this amplifier, together with all the batteries, were housed in a second copper-shielded box suspended below the shielded incubator containing the

embryo. The amplifier, of which a diagram is shown in Fig. 1, was designed primarily to have a low noise level, which is essential if small potential differences, such as the early P-waves, are to be detected. The first tube was mounted in a tight inner compartment of the lower box and was provided with additional sheet-copper shielding. It was also necessary that the first tube of the amplifier should have an extremely low grid current in order to minimize polarization of the electrodes.

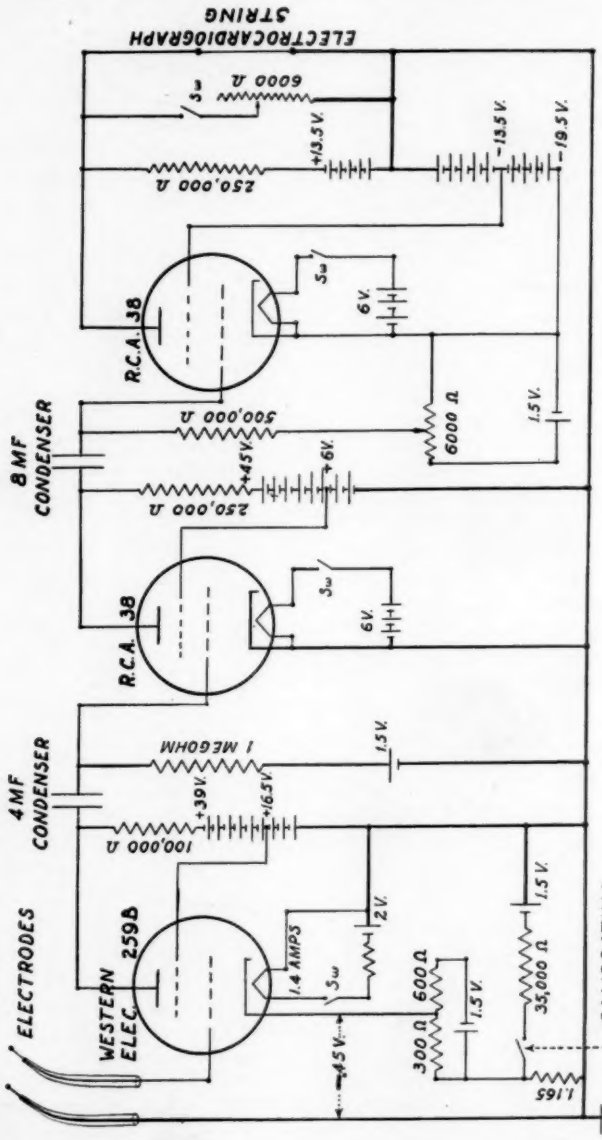

Fig. 1.—Wiring diagram of three-stage, low frequency amplifying system used in conjunction with a Hindle electrocardiograph.

Since the value of an amplifier of this type, used under the conditions of these experiments, depends primarily upon the characteristics of the first stage tube, a number of these were tried. The tube found most satisfactory was Western Electric No. 259B, operated according to the recommendations of Dunning (Pearson,[22] 1934).

It should be emphasized that in using tubes under these unusually exacting conditions each individual tube must be tested, since it is not to be expected that the voltages designated for one will be exactly right even for another tube of the same lot and number. In testing the tubes, characteristic plate current versus grid voltage readings were taken, switching in and out of the grid circuit a resistance of 1.2 by 10^{10} ohms (S. S. White Dental Manufacturing Co.). From the data so obtained two curves can be drawn which cross at "floating grid," when the grid current is zero and when switching in and out of the high resistance has no effect on the plate current. From the divergence of these two curves the magnitude of the grid current at any grid voltage may be calculated. The tubes were studied at various values of heater current, plate voltage, and screen-grid voltage. The 259B tube was operated as follows: Heater current, 1.4 amperes; plate supply voltage, 39; plate voltage, 24; screen-grid voltage, 16.5; grid voltage for floating grid, 0.45. The plate current was 0.15 milliamperes, and the voltage amplification (100,000 ohms plate load) was 24 volts per volt.

The second and third tubes (R.C.A. 38) were used according to the method described by Johnson and Neitzert[23] (1934) except that large, high-resistance condensers were used to adapt the amplifier to heartbeat frequency. The method of balancing off plate current from the galvanometer string is obvious from the diagram. All resistances were wire-wound and soldered in place. Each tube was soldered by the prongs, so that no tube sockets were used, and the electrode, grid, and battery connections were all soldered.

MAJOR CHANGES IN THE STRUCTURE OF THE EMBRYONIC HEART DURING THE PERIOD COVERED BY THE EXPERIMENTS

The embryonic heart, during the early stages of its formation, changes rapidly and radically in structure (Patten,[24] 1922). The initial cardiac contractions in a 29- to 30-hour-old chick take place in a heart which has only its ventricular region well formed. The potential changes one records from a chick in which the heart beats are beginning to develop with sufficient power to set the blood in motion are produced by a heart in which both the atrium and the ventricle have begun to beat, but in which the sinus venosus is still too little differentiated to show any contractile activity. Not until some time after the circulation of blood has been well established does the sinus region begin to pulsate and to take over the pace-making role previously carried by the atrium. With such profound changes occurring in the heart it is obviously futile to attempt any interpretation of records of its action except in the light of explicit knowledge of the morphologic changes with which the physiologic changes are correlated.

The most significant thing about the young embryonic heart, which must be understood in order to interpret the functional changes occurring in it, is the fact that its various regional divisions do not start to differentiate simultaneously, but in sequence. The general manner in which the primitive cardiac tube is formed by the coalescence midventrally of paired primordia which first make their appearance on either side of the midline has long been well known. What

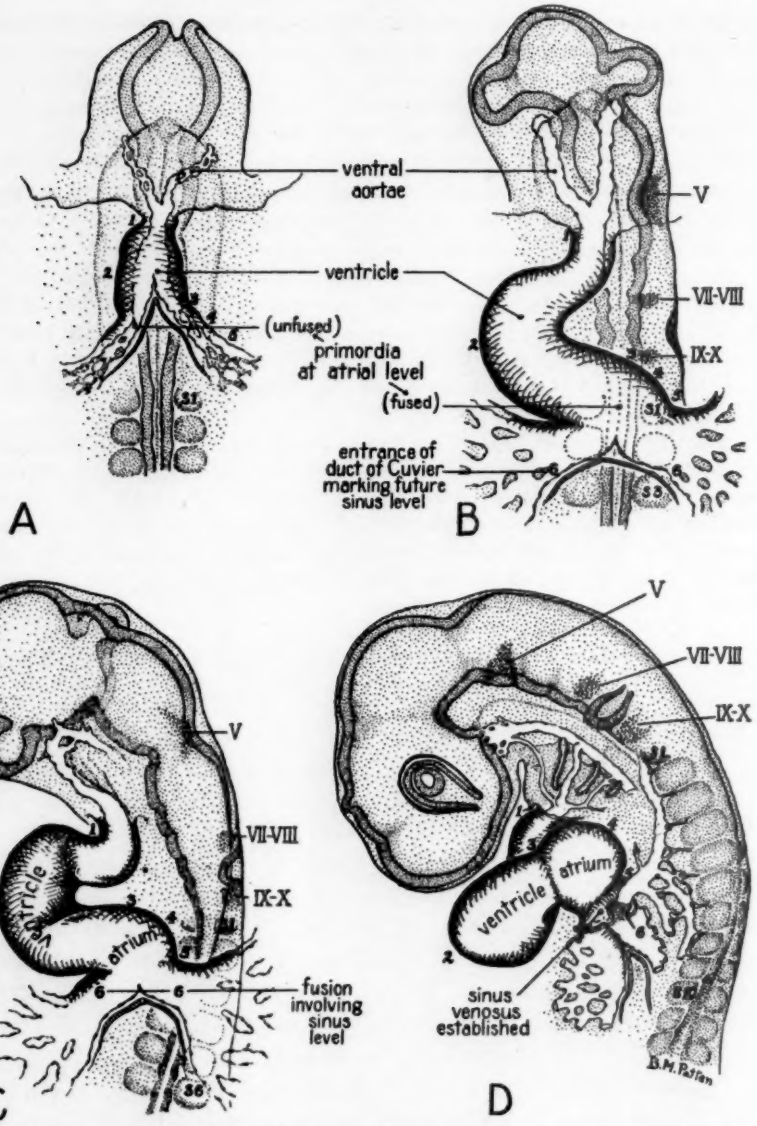

Fig. 2.—The formation of the fundamental regions of the chick heart by progressive fusion of its paired primordia. *A*, at the 9-somite stage, when the first contractions appear. The bulboventricular part of the heart is the only region where the fusion of the paired primordia has occurred and their myocardial investment has been formed. *B*, at the 16-somite stage, when the blood first begins to circulate. The atrium and ventricle have been established, but the sinus venosus exists only as undifferentiated primordial channels, still paired and still lacking myocardial investment. *C*, at the 19-somite stage. Fusion of the paired primordia is just beginning to involve the sinus region. *D*, at the 26-somite stage. The sinus venosus is definitely established and its investment with myocardium well advanced. While schematic as to manner of drawing, these figures are based on projection outlines of actual preparations, and such structures as the somites and the cranial ganglia V, VII-VIII, and IX-X are shown in their exact relationships to serve as landmarks in following the progress of fusion of the cardiac primordia. As an additional aid in following this fusion, arabic numerals have been placed against approximately corresponding locations. The 6 is located at the point of entrance of the duct of Cuvier as determined from injected specimens. Sabin's[31]

(*Legend continued on opposite page.*)

has not until recently received sufficient attention is the fact that the fusion of these primordia takes place gradually, being completed anteriorly before it has even begun posteriorly.

The main steps in the sequential formation of the primary regional divisions of the heart are indicated diagrammatically in Fig. 2. Each of the paired cardiac primordia consists of a delicate endothelial tube flanked laterally by a thickened fold of potentially myocardial tissue. As the endocardial tubes meet in the midline they coalesce with each other to form the endothelial lining of the primitive tubular heart. At the same time the myocardial folds of the two primordia meet each other to complete the outer contractile layer of the heart. If we look at an early stage in this process (Fig. 2 *A*) it becomes evident that, with this fusion beginning, as it does, anteriorly, the bulboventricular part of the heart is established before fusion reaches the atrial level at all. The atrium is formed later, behind the ventricle, as fusion of the primordia progresses caudad (Fig. 2 *B*). Still later the sinus venosus is added behind the atrium (Fig. 2, *C* and *D*).

Myocardial differentiation follows this same sequence, and we find the myocardial layer of the ventricle well formed and considerably thickened, while that of the atrium is still undifferentiated. The atrial myocardium in turn differentiates before that of the sinus. The various regions of the heart begin to beat in the same sequence in which they are formed. Feeble local contractions appear first in the ventricular myocardium and, before the atrium has been fully formed, the ventricle has developed a slow but rhythmic beat of its own. When the atrium has been added behind the ventricle and begins to pulsate, we notice that its contractile rate is higher and that it comes to dominate the slower ventricle, thus increasing the heart rate and initiating a peristaltoid sweep of the contractions from posterior to anterior. It is highly significant that this atrioventricular beat becomes adequate to start the actual circulation of blood before the sinus venosus is sufficiently differentiated to show any contractile activity whatever. It is some time after circulation has commenced that the sinus is formed behind the atrium and in its turn invested with myocardial covering. The sinus, when it becomes active, shows an intrinsically higher contraction rate than either ventricle or atrium, and its incorporation into the cardiac tube again increases the heart rate and lengthens and intensifies the peristaltoid sweep of the contractions.

Legend for Fig. 2 (Cont'd)

Figs. 1 and 2, plate 2, show in dorsal perspective the entrance of the duct of Cuvier at stages corresponding to *B* in this figure. The entrance point of the duct of Cuvier serves as a precise indication of the level of future sinus territory. The heavy black outlines and the crosshatched contours indicate the extent to which the heart is invested by differentiated myocardium. Note especially the absence of anything like an effective myocardial layer encasing the sinus region until a considerable time after the heart has begun to beat and the blood has been set in motion.

A fuller account of the changes outlined above will be found in a paper by Patten and Kramer[21] (1933). The sequential formation of the several regions of the embryonic heart, and the fact that they go into activity in the same order that they are formed is, however, a matter of such fundamental importance for interpreting records of its action that it seemed necessary to summarize this situation briefly here. In comparing records made during this period of rapid changes we must know whether they represent a ventricular beat, an atrioventricular beat, or a sinoatrioventricular beat.

RESULTS AND DISCUSSION

The earliest visible manifestation of cardiac activity occurs in chick embryos at the 29- to 30-hour stage (embryos of nine to ten somites). It consists of spasmodic contractions of small groups of cardiac muscle cells which precede the establishment of regular rhythmic contraction of the heart as a whole. These contractions have been recorded microcinematographically (Patten and Kramer,[21] 1933), and are known to appear first in the primitive ventricular part of the heart. Repeated efforts were made to record the potential changes of these early local contractions but we obtained no satisfactory tracings. This was particularly disappointing in view of the interesting comparison they would have afforded with the potential changes reported by Hogg, Goss, and Cole[25] (1934) for small clusters of cultured ventricular muscle cells from the embryonic heart of the rat.

Our earliest consistent records were from embryos in the 33- to 36-hour range (thirteen to fifteen somites). At this stage of development, fusion of the cardiac primordia has progressed caudad so that it is just beginning to involve the atrial level (Fig. 2 *B*). The heart beat is regular, although still slow in rate, and is beginning to show a peristaltoid character with the beat starting near the atrioventricular junction and sweeping cephalad through the ventricle. Fig. 3 shows the progression of the contraction as recorded by micromoving pictures. An electrocardiographic record taken at this stage is reproduced in Fig. 4.

In the usual electrocardiographic setup, relative negativity of the right-hand electrode produces an upward movement in the tracing. In making our records from the embryonic heart the apparatus was so arranged that the more cephalically placed electrode corresponded to the conventional right-hand electrode. With these facts as to the experimental conditions in mind, and with a timed record of the progress of contraction such as that shown in Fig. 3 for comparison, the general significance of the electrical record seems clear. The initial drop in the tracing indicates the initiation of contraction nearer to the posterior electrode, so that the anterior (right-hand) electrode is first positive. As the impulse moves forward through the ventricle,

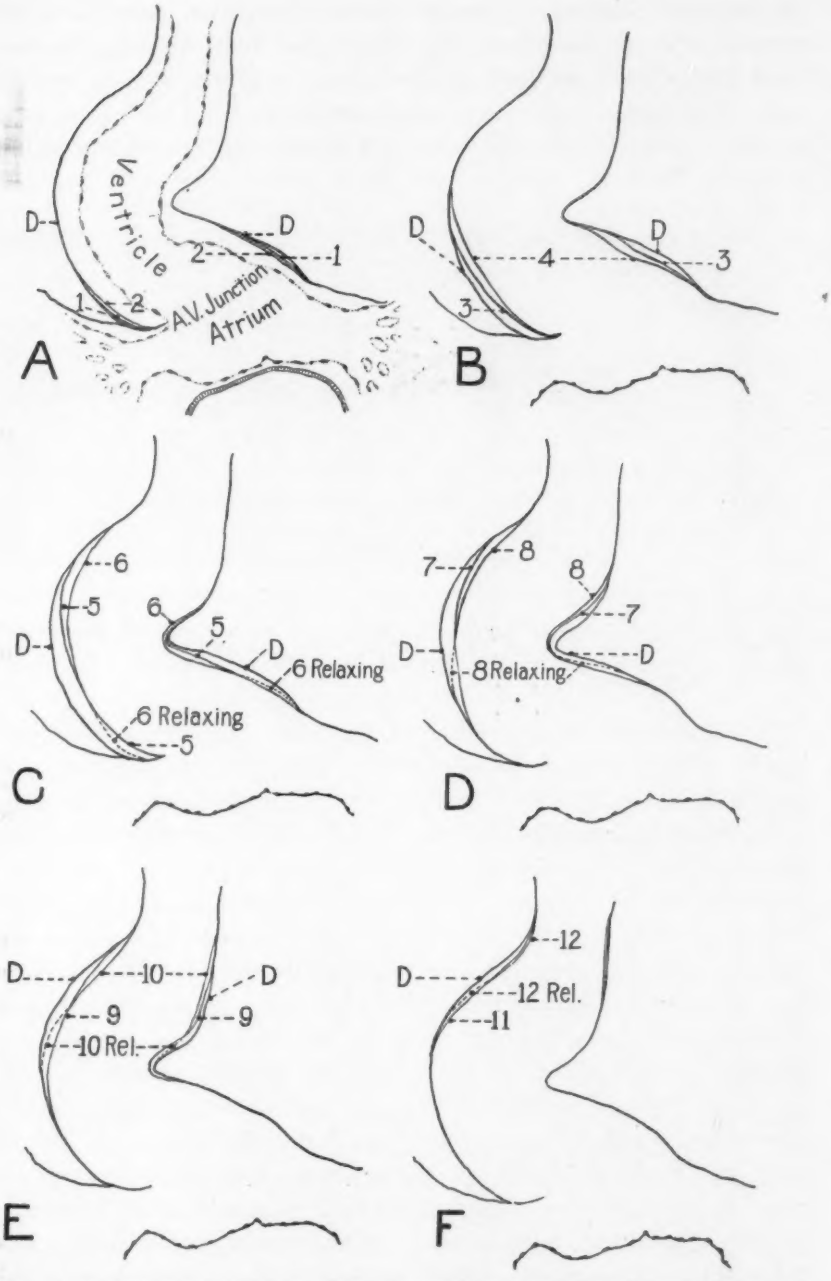

Fig. 3.—Superimposed tracings from micromoving pictures (sixteen frames per second) of heart at stage when the atrium is being established behind the ventricle (12 to 13 somites; ± 32 to 33 hours' incubation). The outer solid line is the tracing of the heart contour during diastole. The numbered contour lines are tracings from successive frames, indicating the contraction changes at one-sixteenth-second intervals during one complete contraction cycle. Where beginning relaxation has brought a contour line nearer to the diastolic outline than the previous frame, the line is drawn broken.

the anterior electrode becomes relatively negative and the tracing sweeps above the isoelectric line. That the initial deflection is downward rather than upward clearly reflects the fact that in the very young embryonic heart the cephalocaudal position of ventricle and atrium is exactly the reverse of that characteristic of the adult, the atrium in the young embryo being more posterior than the ventricle.

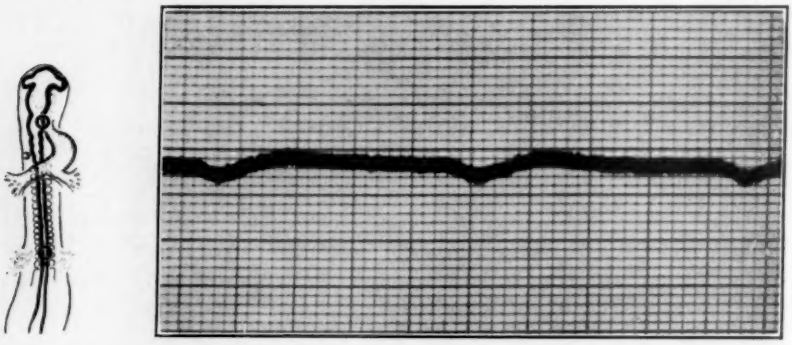

Fig. 4.—Tracing from a 15-somite chick (No. 79, "incubation age" ± 36 hours). Platinized platinum electrodes. Calibration: 50 microvolts = 12 mm.

In this and the following figures the diagram at the left showing the shape and position of the heart was made by projection from a photomicrograph of the actual embryo yielding the record. The small circles indicate the positions in which the electrodes were applied.

The sinusoidal configuration of such tracings from very young hearts calls for additional comment. Almost all the earlier workers in this field have secured tracings of a similar character from "the youngest stages successfully recorded." But repeatedly, as methods have improved, the sinusoidal type of curve has been reported as characteristic of younger and younger embryos, and clear-cut polyphasic tracings have been obtained from embryos of ages at which earlier investigators secured only sinusoidal curves. Eyster, Krasno, and Hettwer[26] (1937) attribute this situation to the fact that with unsatisfactory amplification methods the string had to be unduly loosened to respond at all to the minute potential changes involved. They are inclined to believe that the heretofore reported sinusoidal curves had no significance other than indicating the use of too loose a string. In the light of what has happened in the past, the possibility must be frankly faced that further refinements in technique may result in supplanting with more definite records the sinusoidal curves we obtained from our youngest stages. It is pertinent, nevertheless, to emphasize the fact that our amplification was sufficient to permit taking the record reproduced in Fig. 4 with the string at the normal tightness used for the entire series of observations here reported. Perhaps worthy of comment, also, is the fact that this earliest electrical record of ventricular contraction in the embryonic heart is

strikingly similar to records taken from dying human hearts in the terminal stages of ventricular fibrillation.

Electrocardiograms from slightly older embryos begin to show a sharp downward deflection (Fig. 5) instead of the sinusoidal curve of the earliest records (Fig. 4). We interpret this deflection as being

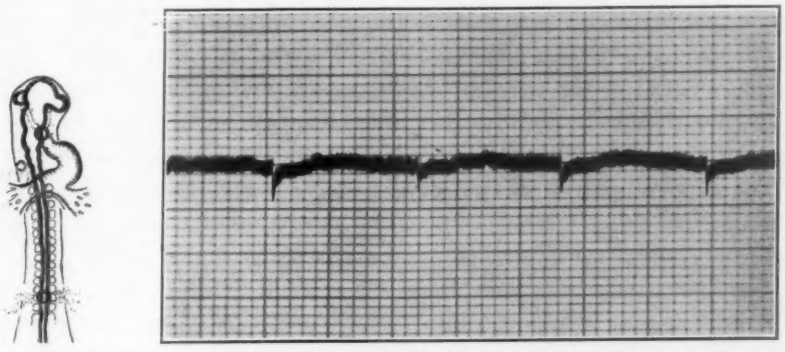

Fig. 5.—Tracing from 16-somite chick (No. 71, "incubation age" ± 38 hours). Platinized platinum electrodes. Calibration: 50 microvolts = 10 mm.

the first manifestation of the QRS or characteristic ventricular complex. There are several points to be considered in arriving at such a conclusion. In the first place, it must be remembered that the heart at this stage is still almost entirely ventricle, and that the atrial region is just beginning to be formed behind the ventricle as fusion of the paired cardiac primordia progresses caudally. Other points of significance can be gleaned from microscopic observation of the character of the heart beats, and from experiments in which the heart is transected at various levels.

When compared with earlier stages, the heart at the stage when this deflection first begins to appear in the electrical records can be seen to have increased its rate, and it will be noted that the individual beats start off decidedly more abruptly. Morphologically, the heart, during this period, has grown in length as fusion of the paired primordia progresses. As the more posterior parts of the cardiac primordia are added to the growing cardiac tube they seem to be bringing in muscular tissue with a higher intrinsic contraction rate than that possessed by the muscle in the more anterior parts of the heart previously formed. This is suggested both by the rate increase which occurs as the heart elongates, and by the fact that the beat becomes more definitely peristaltoid in character with its incipience unmistakably in the posterior part of the heart. The differences in intrinsic contraction rate can be clearly demonstrated by transection experiments. Cuts made in the region which is destined to be the atrioventricular junction seem to yield the sharpest differences in

rate, but regional boundaries are as yet only vaguely suggested and it should not be inferred that there is necessarily any precise level at which there is an abrupt change in inherent contraction rate. Whatever future work may show as to the exact location, and the abruptness of transition in rate, that a gradient in inherent contraction rate exists is beyond doubt. It has been repeatedly demonstrated by cutting experiments (Fano and Badano,[27] 1890; Lewis,[28] 1924; Patten and Kramer,[21] 1933; Paff,[29] 1935) and by physiologic separation of different areas of the cardiac tube by compression (Pickering,[30] 1893; Johnstone,[31] 1924). In the light of such experiments we must conclude that one of the most significant things happening at this stage of heart development is the incorporation into the posterior end of the growing cardiac tube of progressively more tissue with a higher intrinsic contraction rate. As one might expect, the region with the highest contraction rate sets the pace for the heart as a whole. This can be demonstrated, as was done by Paff[29] (1935), by growing the severed parts of a heart in close proximity to each other in culture media and watching the more rapidly beating posterior fragment assume control of the slower beating anterior fragment when a bridge of tissue grows across the cut and places the two pieces again in physiologic continuity. Such an experiment complements beautifully those already discussed in which we have seen the ventricle, when severed from the more posterior part of the heart, revert to the slow nonperistaltoid beat which was characteristic for that region when it was the only part of the heart which had been differentiated and had become active.

Applied to the interpretation of the electrical records reproduced in Figs. 4 and 5, these considerations have led us to conclude that both are records of beats which are still essentially ventricular, although at slightly different developmental phases. The appearance of the sharp downward deflection in the record from the older embryo which was absent in that of the younger we would attribute to the incorporation into the cardiac tube of enough new tissue of higher intrinsic contraction rate to increase the pace of the heart as a whole and to start the contractions off "with a sharp kick." With regional boundaries as vague as they are in such young hearts, it would be unwise to attempt to make any too dogmatic statements as to just how this tissue of higher rhythmicity is disposed with reference to the boundaries which will later be established between atrium and ventricle. The two regions are still at this stage directly continuous, and what little of the future atrial region is formed may well be acting physiologically with the ventricle. In any case there is at this stage so little of the sinoatrial portion of the heart formed and active that one can scarcely regard the action currents obtained as anything else than essentially ventricular.

The next significant change in the character of the records appeared in chicks of about 42 to 44 hours of incubation (twenty somites). At this stage of development fusion of the paired cardiac primordia has progressed caudad to such an extent that the atrial region of the heart is well established and the sinus venosus is just beginning to take shape (Fig. 2 *C*). Records at this stage (Fig. 6) show a small downward deflection coming about two twenty-fifths of a second ahead of the QRS waves. This we believe to be the first appearance of the P-wave. The fact that it is at this stage inverted seems in accord with the fact that the sinoatrial region is still the most posterior part of the heart, so that the impulse is passing toward, rather than away from, the cephalic (right-hand) electrode.

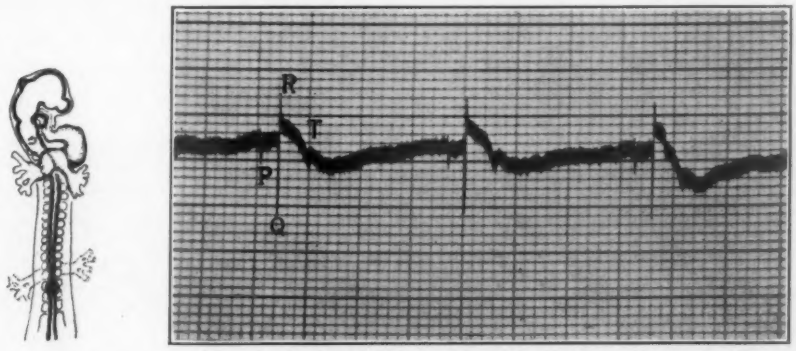

Fig. 6.—Tracing from 20-somite chick (No. 86, "incubation age" ± 42 hours). Capillary glass electrodes, chloridized silver wire embedded in saline-agar gel. Calibration: 50 microvolts = 10 mm.

Between 44 and 60 hours of incubation the configuration of the chick heart is changing exceedingly rapidly. The sinus venosus is definitely formed during this period and the ventricular loop is carried backward into its definitive position posterior to the atrium (Fig. 2, *C* and *D*). During the early part of this period the P-wave is likely to start with a downward throw just as it did when it made its first appearance, but it may end with an excursion above the isoelectric line (Fig. 7). A little later it may be almost unrecognizable (Fig. 8), and still later be entirely an upward throw as it is in the adult (Fig. 9). It seems probable that this apparently erratic behavior of the P-wave can be explained, at least in part, on the basis of the positional changes which are occurring in the heart. At the beginning of this period the beat is starting in the posterior atrial region where the sinus venosus is just beginning to take shape. This is, at this time, the most posterior part of the heart, and an impulse starting there must pass forward into the atrium and thus might be expected to produce an initial downward deflection in the records. The fact that the ventricular end of the atrium at this stage is bent more or less

backward, along with the ventricle, might possibly be the reason for the terminal upward deflection seen in the P-wave of Fig. 7.

The flattening out of the P-wave in Fig. 8 might be accounted for by the fact that with the heart in this stage of loop formation the sinus is becoming more dorsally located while the ventricle projects ventrally. An impulse starting in the sinus and going toward the ventricle would be passing more or less at right angles to a line connecting the electrodes and so produce little departure from the isoelectric line. Following similar reasoning, when the ventricle has come to lie definitely caudal to the sinoatrial part of the heart, the progress of the impulse would be away from the cephalic (right-hand) electrode and the P-wave should appear above the isoelectric line in its characteristic adult form, as was the case in the record reproduced in Fig. 9. It is quite possible, also, that the somewhat more dorsal position of the cephalic electrode used in taking the record of Fig. 9, as compared with that shown in Fig. 8, may have helped to bring out a positive P-wave.

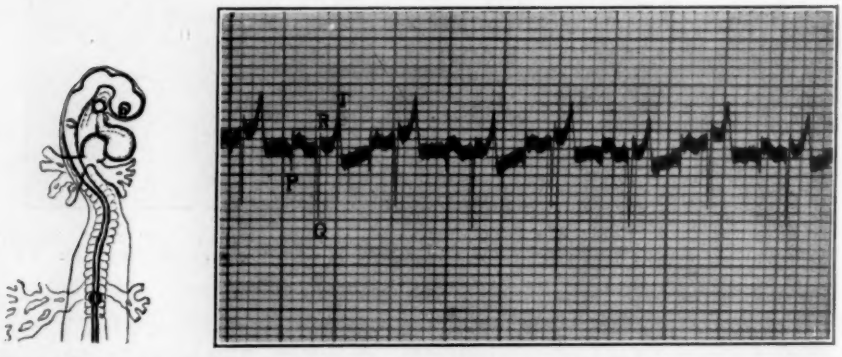

Fig. 7.—Tracing from 24-somite chick (No. 90, "incubation age" ± 48 hours). Capillary glass electrodes, chloridized silver wire embedded in saline-agar gel. Calibration: 50 microvolts = 15 mm.

The rather startling upward deflection shown following the QRS complex in Fig. 9 is puzzling. It appeared quite conspicuously in most of the records taken in this general age range, but was not usually as strongly marked as in this record from chick number 69. Other than the quite obvious fact that it looks like an exaggerated T-wave, we have no suggestion as to its interpretation.

During the fourth day of incubation the electrocardiogram settles into a pattern which is remarkably like that of the adult (Fig. 10). At this stage of development no nerve connections have been made with the heart. In a careful study of serial sections, the nearest to the heart that any migrating neuroblasts were found was in the loose mesenchymal tissue around the dorsal aortic roots. This tends to confirm the opinion of His[32] (1891) that it is certainly not before the end of the fifth or the beginning of the sixth day that the innervation of

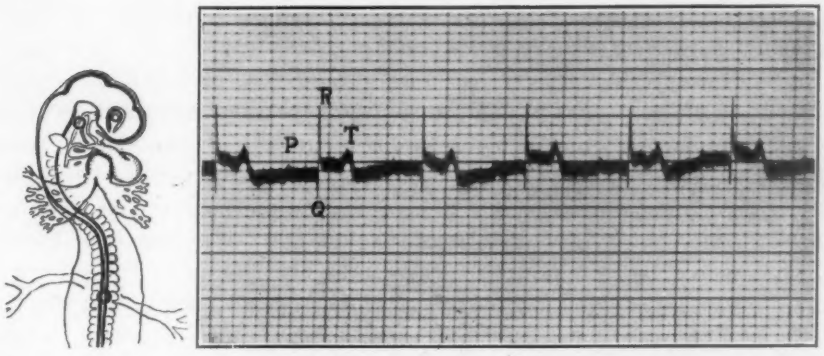

Fig. 8.—Tracing from 31-somite chick (No. 68, "incubation age" ± 61 hours). Platinized platinum electrodes. Calibration: 50 microvolts = 12 mm.

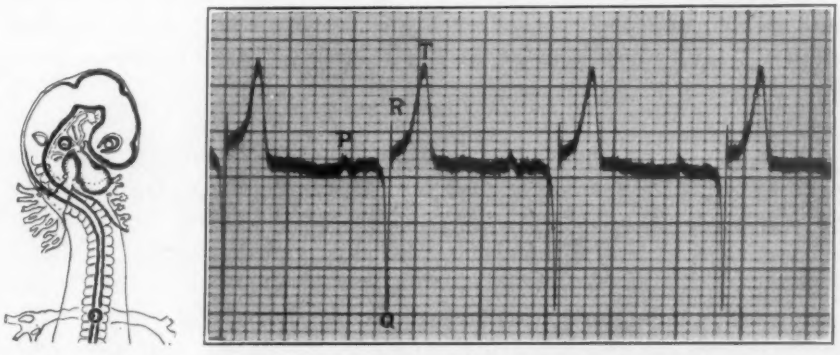

Fig. 9.—Tracing from 29-somite chick (No. 69, "incubation age" ± 58 hours). Platinized platinum electrodes. Calibration: 50 microvolts = 12 mm. Although this embryo had fewer somites than No. 68, its heart is definitely further advanced in the process of loop formation. Such variability in the relative rates at which embryonic structures differentiate is quite common and frequently necessitates, as in this case, an arbitrary sequencing on the basis of the rate of progress in the organ under special consideration.

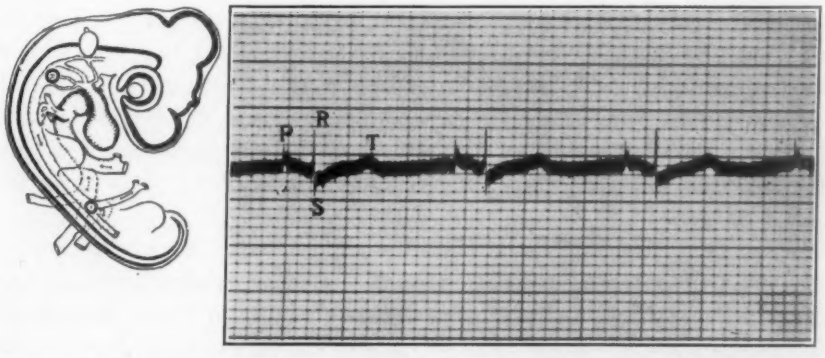

Fig. 10.—Tracing from four-day chick embryo (No. 66). Platinized platinum electrodes. Calibration: 50 microvolts = 11 mm.

the heart is established. Throughout the period covered by the records here presented, therefore, the question of nervous control cannot be raised.

It is of interest, also, that even in the four-day chick heart, which shows a definite atrioventricular sulcus, there has been no separation of atrial and ventricular musculature by ingrowth of connective tissue. It is this secondary ingrowth of connective tissue which, by separating (except for a narrowed bridge in the position of the main His bundle) the hitherto continuous muscle of atrium and ventricle, first makes the sinoventricular conduction system identifiable (His,[33] 1933). It should be emphasized, moreover, that such an identification on the basis of topography can be made a considerable time before it is possible to differentiate the conduction bundle histologically from the rest of the cardiac muscle. In these experiments, therefore, we have been dealing with hearts in which no nerve connections have been established, and the conduction system as we know it in the later stages of the embryo and in the adult has not yet taken shape.

SUMMARY

With the aid of three-stage amplification, electrocardiographic records were made from chick embryos during the early stages of heart development. The youngest embryo from which records were obtained successfully was a fifteen-somite chick. At this stage, which is reached on the average with about 33 to 36 hours of incubation, the nearly straight tubular heart consists almost entirely of ventricle. The electrical record obtained from it shows none of the deflections characteristic of the adult electrocardiogram, but takes the form of a curve which first drops below, and then rises above, the isoelectric line. This configuration is consistent with the posteroanterior direction of the progress of contraction shown by superimposed tracings of successive frames from micromoving pictures of the heart action at this stage.

Slightly older embryos (sixteen to seventeen somites, average incubation age 37 to 40 hours) yield a record in which there appears a sharp downward deflection, followed by a rapid return to, or above, the isoelectric line. Because of its characteristic configuration and because morphologic studies indicate that the embryonic heart at this stage is practically all ventricle, we interpret this as representing the QRS complex.

In the next three or four hours of development, fusion of the cardiac primordia progresses caudally, so that the atrial region becomes definitely differentiated and the sinus venosus begins to take shape posterior to the atrium. Records from embryos in this age range show the appearance of a downward deflection coming about two twenty-fifths of a second ahead of the QRS complex. This we interpret as an inverted P-wave.

During the next day of development the ventricular loop is bent backward so that it comes to be in its adult position caudal to the sinoatrial part of the heart. With this shift in relative positions the P-wave appears above the isoelectric line. Thus by the fourth day of development the electrocardiogram has assumed practically its adult configuration.

It is to be emphasized that not even wandering neuroblasts reach the heart until considerably later in development than the age range covered in these experiments. Furthermore, "conduction tissue" is not at these ages histologically distinguishable from the remainder of the cardiac muscle. Thus we can trace the appearance of all the major features of the adult electrocardiographic pattern in embryonic hearts so young that they completely lack either a nerve supply or a specialized sinoventricular conduction system.

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Department of Clinical Reports

TETRALOGY OF FALLOT: CORRELATION OF CLINICAL, ROENTGENOLOGIC, AND POST-MORTEM FINDINGS

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A TRUE case of tetralogy, as described by Fallot,[1] includes the following: (1) stenosis of the pulmonary artery, (2) enlarged and hypertrophied right ventricle, (3) displaced aorta, and (4) interventricular septal defect. The following case is a typical illustration of the tetralogy of Fallot and offered an opportunity to study the relationship of the chambers and great vessels to one another and to the chest wall.

J. B., a man 20 years old, died of septic endocarditis complicating the tetralogy of Fallot. This patient had been under the care of one of us (J. B. W.) for many years. In the summer of 1933 he developed a septic endocarditis, which was the cause of his death in September of the same year.

A roentgenogram taken three years before death (Fig. 1) reveals the typical cardiac silhouette usually seen in these cases, with blunting of the apex and a roughly rectangular heart.

We were interested in ascertaining what anatomic structures were responsible in our case for the typical cardiac silhouette, and therefore an autopsy was performed in the following manner: On opening the chest by removing the sternum and ribs, the size, shape, and position of the heart and its anatomic relation to the lungs were carefully studied. These organs, together with the liver, were removed *in toto*, and were arranged on the x-ray table in exactly the same anatomic relationship which they had occupied in the body. A cannula was inserted into the superior vena cava and tied to prevent leakage. A large metal syringe filled with barium emulsion was then connected to this cannula and the barium slowly injected until the right auricle was completely filled (seen fluoroscopically). A roentgenogram (Fig. 2) showed complete filling of the right auricle, with some of the barium going through the tricuspid opening. The valve and trabeculae carneae are also visualized. This roentgenogram definitely shows that the right auricle forms the right border of the heart and a goodly portion of its anterior surface. In addition, the inferior vena cava, with its contributing branches, is seen coming from the liver and emptying into the right auricle.

The injection of barium was continued and another roentgenogram taken (Fig. 3). It reveals partial filling of the right ventricle, with some of the barium going into the aorta; as expected, marked narrowing of the pulmonary artery is very evident.

Again we continued the injection of barium until we completely filled the right ventricle (Fig. 4). Here we can see that the anterior surface of the heart is formed almost completely by the right auricle and right ventricle, while only a very small portion of the left ventricle can be seen. The apex is blunted and is formed com-

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pletely by the right ventricle, instead of the left, as in normal hearts. Again the marked stenosis of the pulmonary artery is very evident and the aorta contains more barium. After roentgenograms of the right heart were taken, the organ was washed out as well as possible and a hypodermic needle substituted for the cannula (superior vena cava) as a landmark. The cannula was then inserted into one of the pulmonary veins and another roentgenogram taken (Fig. 5). The barium-filled syringe was connected to the cannula and the material slowly injected until the left auricle was

Fig. 1. Fig. 2.

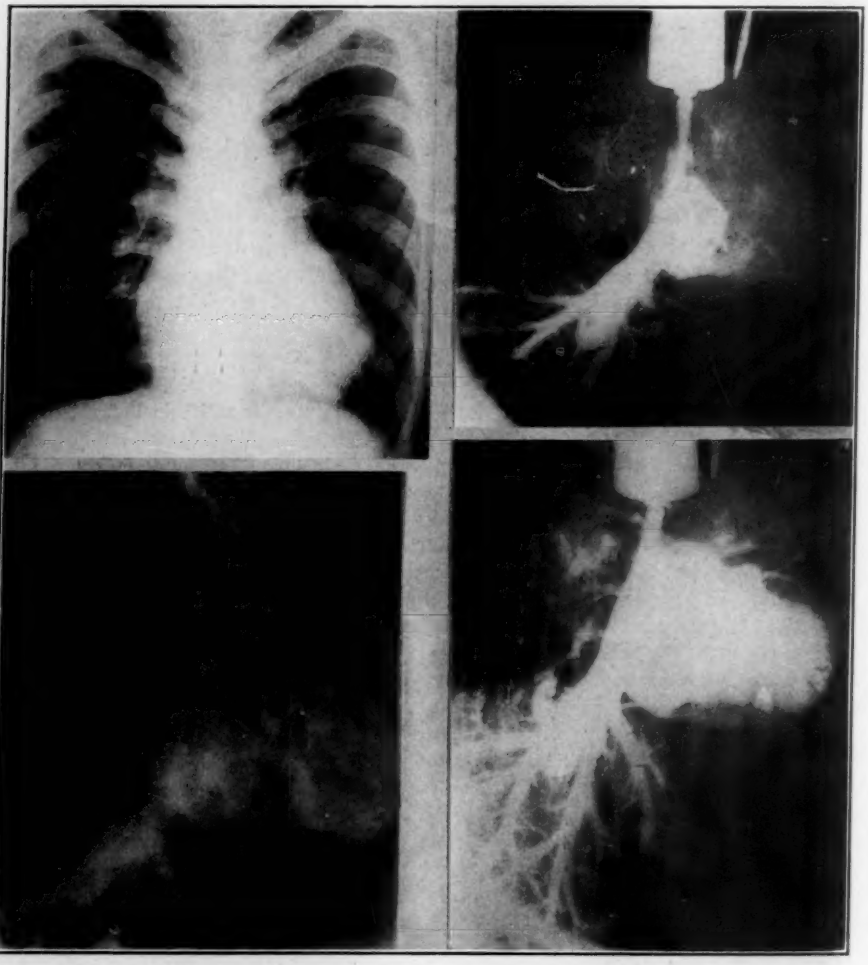

Fig. 3. Fig. 4.

filled (Fig. 6). This roentgenogram shows the filled-out left auricle with some of the material going through the mitral opening into the left ventricle, and some going through to the aorta. The pulmonary and hepatic arterial trees are also shown. If Fig. 2 be superimposed upon Fig. 6, it will be seen that the left auricle occupies a position posterior and somewhat medial to the right auricle. The injection of barium was then continued until the left ventricle was completely filled (Fig. 7). This roentgenogram shows that the left ventricle lies almost entirely behind and is

small as compared to the right ventricle. It is also very interesting to note that, although there exists an opening in the membranous portion of the interventricular septum, the barium fails to go into the right ventricle. It may be possible that nature prevents the blood from going from the left to the right ventricle by developing the moderator band, which may act as a valve in closing off the septal opening

Fig. 5. Fig. 6.

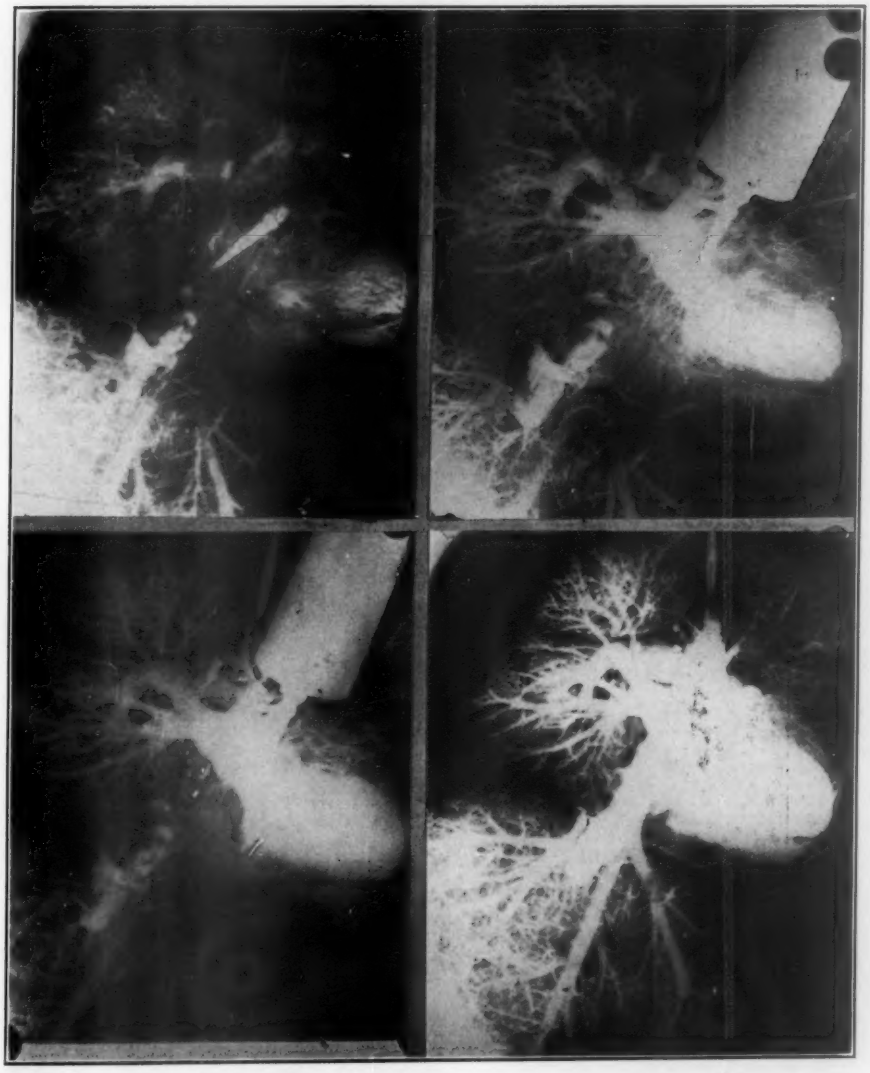

Fig. 7. Fig. 8.

during cardiac systole. The barium was then forced in under great pressure and Fig. 8 taken. This shows that under pressure the barium finally went through the interventricular opening into the right ventricle, and then into the pulmonary artery. Next, the heart was dissected and washed and a window cut into the right ventricle (Fig. 9). This shows the enlarged right ventricle with its hypertrophied

Fig. 9.

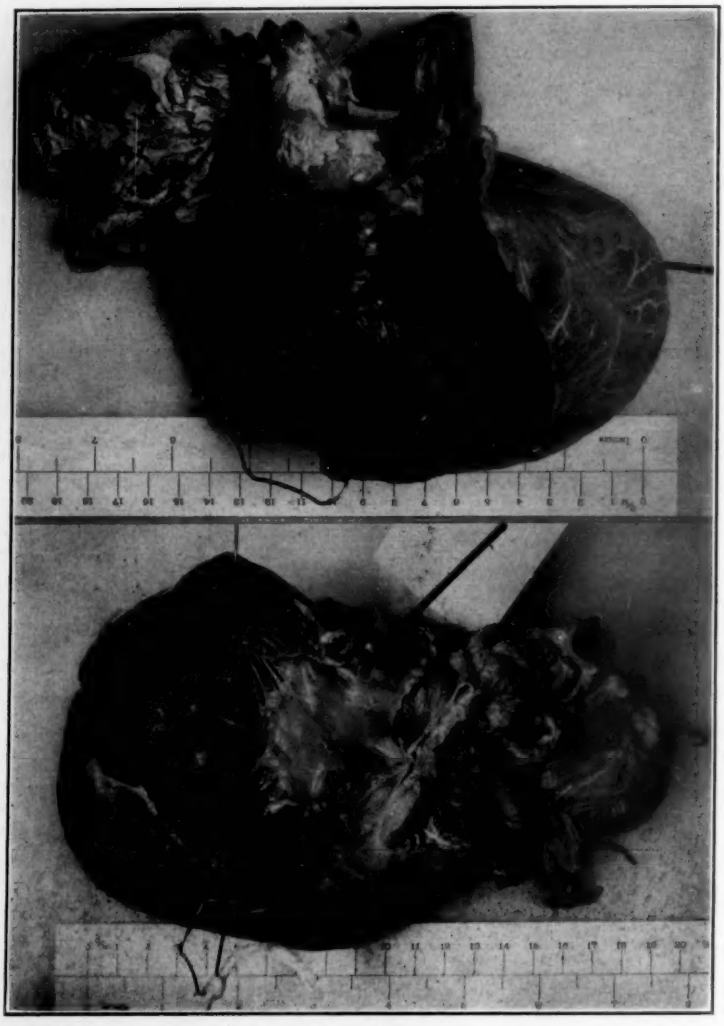

Fig. 10.

walls and, in addition, the interventricular opening with the displaced aorta and stenosed pulmonary artery. A window was then cut into the left ventricle (Fig. 10), showing the small size of this chamber as compared to a normal one; a probe which is running through the interventricular opening is also seen. Finally, a drawing of the anterior aspect of the heart was made in such a way that the picture was a trifle smaller than the original. This was then superimposed on a roentgenogram taken ante mortem (Fig. 11), in order to show the reason for the typical silhouette and the position of the various chambers.

COMMENT

From a diagnostic point of view, Blackford[2] stresses the rectangular appearance of the heart and its increased transverse diameter. He also

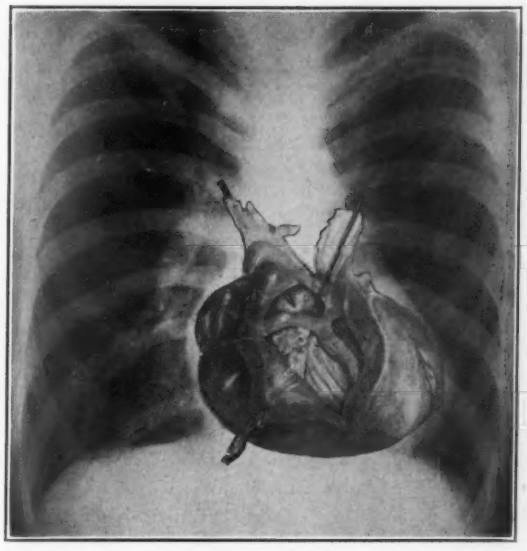

Fig. 11.

points out that the apex of the heart is formed entirely by the right ventricle, instead of by the left, as is the case in the normal heart. These observations deserve emphasis as an aid in the diagnosis of this condition. We attach significance to the blunted appearance of the apex roentgenographically.

Popp[3] establishes the following criteria for the roentgenologic diagnosis of tetralogy of Fallot: (1) Absence of the pulmonic conus as a sign of hypoplasia of the pulmonary artery; (2) deviation of the vascular pedicle to the right—*aorta du cheval;* (3) masking of the aorta by the trachea in the right anterior oblique position, and (4) crossing of the aorta by the right bronchus.

Abbott,[4] largely on the basis of the studies by Sir Arthur Keith, ascribes the lesions of the tetralogy of Fallot to an arrest of development of the cardiac apparatus before the eighth week of embryonic life.

CONCLUSION

We have presented a case of tetralogy of Fallot, and have endeavored to show which anatomic structures are responsible for the typical cardiac silhouette.

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MERCURIAL DIURETICS IN CARDIAC FAILURE

Report of a Case in Which Three Hundred Forty-Three Injections Were Given*

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BECAUSE there is still some fear in the minds of practitioners regarding the possibility that repeated injections of mercurial diuretics may have deleterious effects, I am reporting the following case of a patient who received 343 injections of salyrgan and mercupurin over a period of seven and a half years without evidence of any harmful effect.

Dixson[1] reported a case in which 150 injections were given; Maxwell, Scott, and Harvey[2] reported one in which 198 were given; Levine[3] reported one in which 250 were given; and Wiseman[4] reported another in which 270 were given.

REPORT OF CASE

L. R., a white man 48 years old, was admitted to Mt. Sinai Hospital Sept. 2, 1930, as a private patient of Dr. Harry J. Kumin, and then transferred to the Medical Service of Dr. Samuel S. Berger. On admission the patient presented the typical clinical and electrocardiographic findings of acute coronary occlusion. In February, 1931, he was admitted to the Cardiac Clinic with signs of congestive failure, and he continued to have more or less cardiac failure from this time until his death on April 20, 1938. During this period the patient was admitted to the hospital eight times for increasing degrees of failure; several of the exacerbations were thought to be due to fresh coronary occlusions.

During the period from October, 1930, to April, 1938, this patient received a total of 343 injections of salyrgan and mercupurin in doses varying from 2 to 4 c.c. The injections were given intravenously until obliteration of all accessible veins forced us to use the intramuscular route. The response to these mercurial diuretics remained good throughout, and attempts to discontinue their use were attended with such an increase of the edema and visceral congestion that the patient would literally beg for the injections (unpleasant as they were after they had to be given intramuscularly).

In addition to the above, the patient was kept on a maintenance dose of digitalis, and the action of the mercurial diuretics was augmented at different times by the administration of ammonium chloride, ammonium nitrate, potassium chloride, and aminophyllin.

The urine contained small amounts of albumin throughout, with casts occasionally. On Nov. 19, 1936, the nonprotein nitrogen of the blood was 38 mg. per 100 c.c., and the creatinine 1.6 mg. per 100 c.c. Unfortunately, the obliteration of the patient's veins by the frequent mercurial injections made it impossible to obtain further samples of blood for chemical examination. However, examination

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of the urine a short time before death (March 21, 1938) showed only a trace of albumin and a few leucocytes.

The patient died suddenly at home, and permission for an autopsy could not be obtained.

SUMMARY

A case is reported of a patient who received 343 injections of salyrgan and mercupurin over a period of seven and a half years without any deleterious effect.

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FATAL HEMORRHAGE FROM A PERSISTENT RIGHT DORSAL AORTA TERMINATING IN THE LOWER LOBE OF THE RIGHT LUNG

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ANOMALOUS branches of the descending aorta arising in the immediate proximity of the diaphragm are apparently rare. In a search of the literature no report of an aortic branch similar to that described below was found.

The case considered is that of a child who died of pulmonary hemorrhage from an anomalous branch of the aorta. The artery arose from the abdominal aorta immediately below the diaphragm and terminated in the inferior portion of the lower lobe of the right lung.

REPORT OF CASE

The essential history is that of repeated pulmonary hemorrhages occurring in a 10-year-old male negro over a period of two years. For this reason the child was admitted to the Children's Hospital of Pittsburgh on Oct. 20, 1937, and again on Nov. 18, 1937. The hemorrhages recurred at intervals of from two weeks to two months. Occasionally they occurred during sleep, and at other times appeared to have been precipitated by excitement or physical exertion. The amount of blood lost each time varied from approximately 200 to 400 c.c. There were no significant abnormal physical findings other than those indicating consolidation of the lower lobe of the right lung and secondary anemia. The roentgenogram showed a large area of consolidation below the hilum of the right lung. A severe secondary anemia was present. On the first admission examination of the blood gave the following results: hemoglobin 34 per cent; red blood cells 1,950,000; white blood cells 8,600; neutrophiles 82 per cent; lymphocytes 18 per cent; reticulocytes 0.9 per cent. A moderate amount of anisocytosis and poikilocytosis was present. Frequent transfusions diminished the degree of the anemia. The temperature remained at about 99° F. The pulse rate varied between 90 and 105; this tachycardia was probably due to the secondary anemia.

The history, physical findings, roentgenogram, negative tuberculin test, negative blood Kahn reaction, and anemia suggested as possible primary diagnoses lung abscess, bronchiectasis, or a growth obstructing a bronchus.

Death finally resulted from a massive hemorrhage. Autopsy showed that death was caused by rupture of an anomalous branch of the aorta within the lower lobe of the right lung, followed by aspiration of blood into the alveoli.

Autopsy Findings.—The only significant pathologic changes found at autopsy were confined to the chest. The pericardial sac was somewhat dilated and contained 150 c.c. (estimated) of clear straw-colored fluid. The heart was somewhat dilated with respect to all its chambers. It measured 11 by 7 by 5 cm. and weighed 207 gm. The cut surface of the cardiac muscle was of a dusky-red hue. The mitral orifice measured 7.5 cm. in circumference, the tricuspid 9 cm. Both easily admitted the index finger. The aortic ring measured 5.5 cm., the pulmonary 6 cm., in circum-

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ference. The valves contained the normal number of leaflets, and there was no evidence of vegetations or of any sclerosis. The common carotid and subclavian arteries seemed slightly larger than normal. The ductus arteriosus and foramen ovale were closed. Upon dissecting out the descending aorta, a large branch, measuring 1.0 cm. in diameter, was found arising from the right side, just posterior and inferior to the diaphragm. This branch coursed almost vertically upward to enter the diaphragmatic surface of the lower lobe of the right lung near its posterior margin. Within the lower posterior portion of this lobe there was a firm mass about 4 cm.

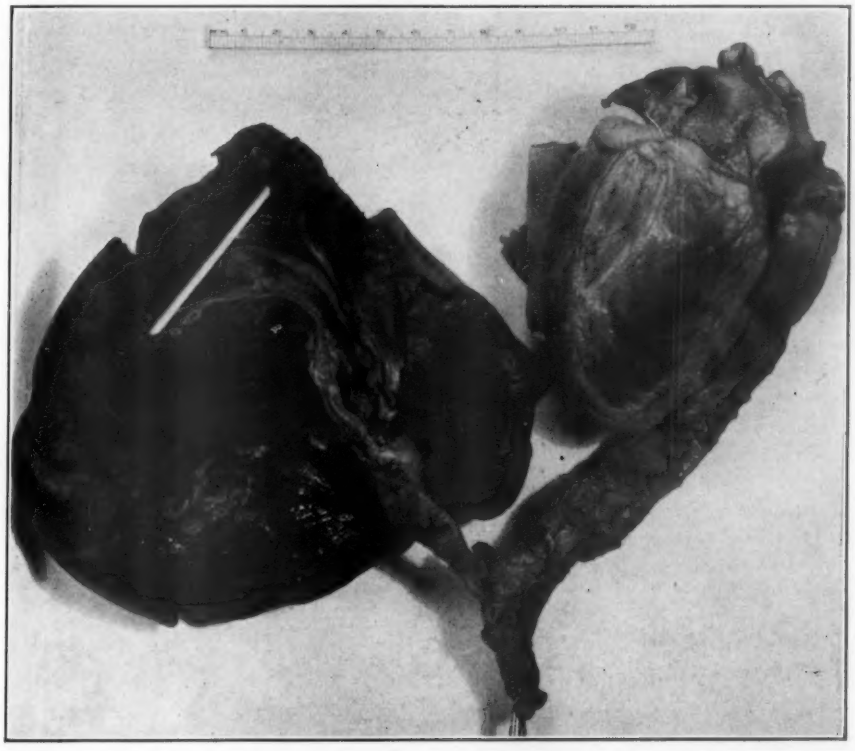

Fig. 1.—Photograph showing heart and anomalous artery leaving the descending aorta and entering the inferior surface of lower right lung lobe. The relative position of the lung has been disturbed in order to show the manner of entrance of the anomalous artery. Note the vessel does not enter at the hilum.

in diameter which was dark red in color. The anomalous vessel described above entered the inferior surface of this mass. Upon longitudinal section of this vessel it was found that it terminated within the middle of the mass as a network of rather large-calibered vessels, which apparently ended blindly. The lumina of these vessels were filled, in many instances, with organized clot. The vessels lay in close relationship with the bronchioles. No direct communication between vessel and bronchiole was found, although such a communication must have existed. The apex of the left lung was attached to the parietal pleura by fibrous adhesions. Throughout the left lung and the upper and middle lobes of the right lung there were scattered hemorrhagic areas, measuring about 1 cm. in diameter, which were fairly uniformly distributed. The cut surface showed that the alveoli were filled with blood. Microscopic examination showed that the main pathologic changes were in the lungs. In some areas the alveoli were filled with blood; in others there was compensatory emphysema. In

the blood-filled alveoli there were numerous large macrophages which contained blood pigment and particles of carbon. A few similar macrophages were found in the bronchioles. The alveolar walls of the air-containing sections were thickened because of the presence of congested capillaries, small round cells, and a few neutrophiles. The anomalous artery showed some early atheromatous changes in the deeper layers of the intima.

DISCUSSION

Two possibilities as to the developmental origin of this vessel have been considered. The first is that this anomaly may have arisen from the distal portion of a persistent right dorsal aorta. The second possibility is that this anomaly may have originated from the persistence of both the right dorsal aorta and one of several of its branches. These branches include the dorsal part of the sixth (pulmonary) arch and a series of branches of the right dorsal aorta which arise caudad to the sixth arch and enter a capillary network in the developing lung.

Orientation with respect to the anlage of the anomaly may be obtained by a brief review of some features of the development of the aortic arch system. Early in development there exists an arterial trunk, or sac, located ventrally in the embryo. From this trunk there proceed two vessels which arch dorsally and then extend caudad. These two vessels are the right and left dorsal aortas (Fig. 2). The left dorsal aorta forms the greater part of the descending aorta of the adult. The right and left fuse for some distance at their caudal extremities (Fig. 2). The unfused portion of the right aorta, distal to the final origin of the right subclavian artery, normally becomes obliterated[1, 2] (Fig. 2).

This anomaly may be ascribed to failure of the above-mentioned obliteration of the right aorta to occur. Normally the caudal portions of the two dorsal aortas fuse as a result of an initial connection by transverse capillary anastomoses between the two vessels.[2] The highest cranial level at which the two paired aortas fuse and then proceed as one vessel is known as the region of bifurcation[1] (Fig. 2). It is at this level that the vessel in the case here reported should have arisen. In attempting to place the ultimate level of the region of the bifurcation of the aorta in the human embryo, Congdon[2] says: "It is probable that a rather common type of anomalous subclavian described in the adult indicates roughly by its origin the ultimate position of the region corresponding to the former bifurcation." These anomalous subclavians are associated with a failure of the caudal part of the paired right aortas to become obliterated.[1, 2, 3] In this respect their origin is similar to the vessel under discussion. According to Congdon[2] "(Abnormal) subclavians of this kind are found in the adult arising from the termination of the arch or the aorta as far caudal as the fifth thoracic vertebra. Since the subclavian and other branches of

the arch shift cranially upon it (the aorta), there is a possibility that the aortic wall derived from the earlier region of the bifurcation lies still lower."

It is unfortunate that at the time of autopsy we did not accurately determine the vertebral level of the origin of the anomalous vessel. Roughly, however, it arose at the level of the second or third lumbar vertebra. This level, then, is in harmony with Congdon's concept that at some time the level of the bifurcation of the aorta lies lower than the fifth thoracic.

It seems probable that the network of vessels within the lung tissue had its origin in the postbranchial pulmonary plexus (Fig. 3) which had maintained connection with the persistent right dorsal aorta by one of its several branches. These branches include the dorsal root of the right sixth arch (Figs. 2 and 3) and a series of six additional branches which in the embryo are found arising from the dorsal aorta caudad to the sixth arch (Fig. 3).

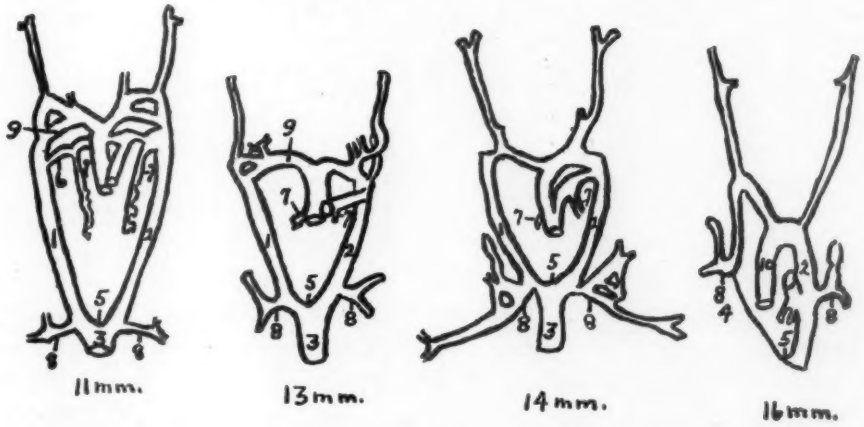

Fig. 2.—From Congdon, E. D.: Contributions to Embryology, Carnegie Institute of Washington Publication No. 14, 47, 1922 (slightly modified). Ventral views of aortic arch system, showing successive developmental stages in human embryo: *1*, right dorsal aorta; *2*, left dorsal aorta, the descending aorta in the 16 mm. embryo; *3*, fused portion of right and left dorsal aortas; *4*, the obliterated right dorsal aorta, the probable origin of the anomalous vessel here discussed; *5*, region of bifurcation of the aorta placed at the level of the second or third lumbar vertebra in the case here considered; *6*, dorsal root of the sixth arch which becomes obliterated in process of normal development; *7*, pulmonary arteries; *8*, subclavian arteries; *9*, fourth right arch; *10*, ascending aorta.

The embryology of the sixth arch and the aortic branches which enter the pulmonary plexus may be summarized briefly as follows: In the embryo the ventral arterial trunk and the two dorsal aortas are connected by a series of paired arches. Each arch, with the exception of the transient fifth, contributes in part to the adult arterial system. It is with the sixth that the discussion here is concerned. The sixth arch is tapped on either side by a branch from the pulmonary plexus of vessels.[4, 5] These branches develop into the pulmonary

arteries. The part of the left sixth arch distal to the origin of the branch forms the ductus arteriosus, later the ligamentum arteriosus. The corresponding distal part of the right sixth arch becomes obliterated entirely in normal development (Fig. 2). Failure of this portion to become obliterated and a persistence of its connection with the right dorsal aorta is therefore ventured as one explanation for the peculiar pulmonary termination found in this case.

Fig. 3.—From Huntington, G. S.: The Anatomical Record 17: 165, 1919-20 (slightly modified). Right side of 4 mm. cat embryo: *A*, aorta; *1* to *6*, aortic arches; 7 to *10*, branches of the thoracic aorta entering postbranchial pulmonary plexus; *L*, pulmonary anlage.

With regard to the sixth arch and the other vessels which connect the aorta and pulmonary plexus in the embryo, Huntington[5] has the following to say: "The dorsal rudiment of the sixth arch arises from the dorsal aorta, extending craniad as a short spur. This I shall designate as the cranial member in a series of aortic derivatives which, inosculating in a capillary network, form what may be defined as the postbranchial pulmonary plexus (Fig. 3), in view of the part it takes in the development of the pulmonary artery _____. The succeeding two components *(7, 8)* follow in close proximity to 6, _____. The ninth aortic derivative enters the plexus considerably further caudad _____." Further dorsal aortic tributaries in the cat embryos described by Huntington numbered as many as twelve. Of older embryos Huntington[5] says: "The plexus as a whole is in the process of abandoning its primary multiple aortic connections and of transferring to the new line of the future pulmonary artery, initiated by its junction with the caudal spur from the ventral segment of the sixth arch." A persistence of one of these branches of the right dorsal aorta may offer a satisfactory explanation for the pulmonary termination of the persistent right dorsal aorta.

SUMMARY

A case of an anomalous branch of the descending aorta arising below and close to the diaphragm has been described. Its probable origin as a persistence of a part of the right dorsal aorta or of this vessel together with one of its early pulmonary branches has been discussed.

I wish to thank Dr. Maud L. Menten, Pathologist to the Children's Hospital of Pittsburgh, for the privilege of presenting this case and for the guidance which has made this discussion possible. Dr. Maude E. Abbott, in a personal communication with Dr. Menten, has confirmed the concept that this anomalous vessel arose from the right dorsal aorta.

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CONGENITAL ATRESIA OF THE AORTIC VALVE WITHOUT SEPTAL DEFECT

Report of Case

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MANY slight developmental anomalies of the heart, such as a persistent foramen ovale or ductus arteriosus, are not associated with a definite clinical picture and are therefore of no particular practical interest. In these cases the cardiovascular changes which normally take place shortly before or after birth are delayed for a variable period. They represent, therefore, simply transient arrests in development. In contrast to this group, the following unusual case is reported because it combines a number of true errors and defects in development of the heart and its great vessel attachments. The outstanding feature was complete atresia of the aortic valve with hypoplasia of the ascending aorta. Only seven such cases have been collected in a review of the recent literature. An analysis of a total of 4,364 post-mortem examinations performed at the McGill Pathological Institute from 1919 to 1933 disclosed thirty-five cases of congenital heart anomalies (Table I). In this series there were only two instances of complete aortic atresia, one of which is herewith recorded.

Analysis of Thirty-Five Autopsy Cases of Congenital Heart Disease

1. Defects of Interauricular Septum	
Patent foramen ovale	2
2. Defects of Interventricular Septum	
At base without dextroposition	6
Defects elsewhere, or multiple	5
3. Complete Defects of Cardiac Septa	
Cor triloculare biatriatum	2
Cor biloculare	1
4. Transposition of Arterial Trunks	
Complete transposition	
Closed interventricular septum	2
Defect interventricular septum	1
5. Pulmonary Atresia	
With closed interventricular septum	1
6. Aortic Stenosis and Atresia	
Aortic stenosis	4
Aortic atresia	1
7. Anomalies of Semilunar Cusps	
Bicuspid aortic valve	2
Defect of aortic valve	1
8. Tricuspid and Mitral Stenosis	
Mitral atresia	2
9. Anomalies of Auriculoventricular Cusps	
Defect tricuspid valve	1
10. Hypoplasia of Aorta	3
11. Anomalies of Great Veins	
Pulmonary	1
Total	35

*From the Pathological Institute of McGill University, Montreal. Prof. Horst Oertel, Director.

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A satisfactory classification of congenital heart disease is difficult. This is not only because a great variety of anomalies may occur, but also because some are complicated by intrauterine infections. A classification based on a correlation of the clinical and anatomic facts has been outlined by Abbott,[1] and this has been applied to the findings in this case.

REPORT OF CASE

Clinical Note.—The clinical course was very brief. The baby was delivered spontaneously; it was a breech presentation. The mother was a well, active woman, giving no history of infection. For the first three days following birth the baby was apparently normal, and then suddenly refused to nurse. He died seventy-six hours after he was born. There was at no time any cyanosis or dyspnea. The physical examination revealed no murmur, thrill, or any other evidence of cardiac defect. The liver was palpable, but not the spleen. A lumbar puncture was performed and blood was found in the cerebrospinal fluid, but this blood was thought to have been introduced by the puncture. Adrenal hemorrhage was suspected as the cause of death.

Abbreviated Protocol.—Case 17626, Autopsy No. 162-34. (The autopsy was performed forty-two hours post mortem.) The body was that of a large, well-nourished baby, 51 cm. long and weighing 3,640 gm. There was no edema. Postmortem lividity was diffuse. The thorax was symmetrical and the abdomen rounded. The center of ossification was present in the lower end of both femurs.

On opening the thorax, the transverse diameter of the precordium measured 6 cm. and that of the pericardium 7.5 cm. The thymus was large, pinkish-red, lobulated, and contained scattered petechiae. The trachea contained a small amount of curd. The lungs were of usual size, shape, and consistency. They were smooth, glistening, crepitant, elastic, and pinkish-red, both on pleural and cut surfaces. The bronchi were free, with light red mucosa. These represent normal findings for this age. The heart is subsequently described in detail.

On opening the abdomen, the subcutaneous fat was 1 cm. thick. The liver was 4 cm. below the costal angle, 5 cm. below the right costal, and 2 cm. below the left costal margin, in the midclavicular line. The diaphragm extended to the fourth intercostal space on both sides. The spleen weighed 20 gm.; its capsule was smooth and glistening and it was dark red. The cut surface showed gray, prominent, lymph follicles surrounding the dark red hemorrhagic pulp. The kidneys weighed 20 gm. each and were similar. The capsule stripped readily, revealing a red, smooth surface with fetal lobulations. The cut surface showed a pale red cortex with darker medulla, each in normal relation. The bladder was empty; its mucosa was smooth and white. The testes were normal. The stomach and large and small intestines had an intact, pale gray mucosa. The pancreas showed no anatomic lesion, and the adrenals were markedly autolyzed. The liver weighed 170 gm.; its capsule was smooth and glistening, and it was dark reddish-brown with large intermingled white to yellow patches. Its thin margins were rounded. The cut surface was brown, with similar indistinct yellow and red mottled areas. The brain weighed 450 gm. On section, after formalin fixation, it showed no anatomic lesion. The middle and internal ears were intact and free of gross exudate.

Heart.—The pericardium was smooth and glistening. The weight of the heart was not obtainable because of its attachment to the other thoracic structures. The myocardium was firm and reddish brown. In situ, the right auricle appeared dilated and hypertrophied, with a notably dilated auricular cavity. The septal,

marginal, and infundibular cusps of the tricuspid valve were well formed and not thickened. The valve measured 5 cm. in circumference. The patent foramen ovale measured 1 cm. in diameter. The right ventricle was also dilated. It occupied the whole apex and measured 1 cm. in thickness. The columnae carneae were large, producing a marked fenestration of the wall of the chamber. The papillary muscles were hypertrophied. The pulmonary valve was intact and its sinus appeared dilated. The pulmonary artery was large, thick-walled, 3 cm. in circumference, and definitely dilated. The ductus arteriosus was widely patent, measuring 1.3 cm. in circumference, and was definitely dilated; it entered the aorta in its usual position.

The left auricle was small. The intima was smooth, pale gray and appeared thickened; a single pulmonary vein entered it on either side. The mitral valve was very hypoplastic and was 1 cm. in diameter. There was complete fusion of the leaflets, forming an irregular, pale gray thickening, covered with numerous granular, smooth, gray, pinhead elevations. The chordae tendineae were well defined, very delicate, and inserted directly into the myocardium, except for a rudimentary papillary muscle attached to the chordae of the posterior leaflet. The left ventricle formed a round cavity about 1.2 cm. in diameter, having a smooth, pearly-gray endocardial surface and a wall 8 mm. thick. The aortic valve was represented only by a dimpling at the base of this cavity, indicating the complete aortic atresia. The ascending aorta extended directly upward for 2.4 cm. as a thin, well-formed, but hypoplastic artery, only 4 mm. in circumference. It was continuous with the innominate artery, which was slightly larger than the aorta and much thicker-walled. The arch branched directly to the left, giving off normal-appearing left common carotid and subclavian branches.

The coronary arteries came off at the usual places. The left descending coronary artery extended down the left side of the interventricular septum, and the right appeared to anastomose with it on the opposite side. The apex of the very small left ventricle was situated 2.2 centimeters above the apex of the heart, which was therefore formed completely by the right ventricle.

Histologic Examination.—The right ventricle of the heart showed slight hypertrophy of the muscle fibers, with a thin endocardium. The left ventricle showed a hyaline, fibrous tissue thickening of the endocardium, with no cellular exudate. This fibrous tissue tended to surround the small vessels in the adjacent half of the myocardium and represented a sclerosing productive endocarditis which extended slightly into the adjacent myocardium. The sections of all other organs showed no anatomic lesion.

Anatomic Diagnosis.—Hypertrophy and dilatation of the right heart; patent ductus arteriosus and foramen ovale; hypoplasia of the left auricle and ventricle; hypoplasia of the mitral valve; *complete atresia of the aortic valve* and hypoplasia of the ascending aorta; productive endocarditis involving the entire left ventricle.

DISCUSSION

The appearance of the heart suggested that the anomalies might have been caused by a deviation to the left in the growth and fusion of the interventricular septum with the structures at the base. The right auricle and ventricle were therefore largely responsible for maintaining the systemic fetal circulation through the patent ductus and foramen ovale. Compensatory hypertrophy and dilatation of these chambers were the inevitable result.

In the normal course of the fetal circulation, the oxygenated blood from the placenta passes by the umbilical vein partly into the hepatic circulation, and the rest, by means of the ductus venosus, into the inferior vena cava and thence into the right auricle. The patent foramen ovale then allows the blood to flow successively into the left auricle and ventricle, whence it is propelled into the aorta. The blood from the superior vena cava passes through the right auricle into the right ventricle and thence by the ductus arteriosus into the aorta beyond the origin of the left subclavian artery. A small quantity also goes through the pulmonary artery. Normally, the ductus arteriosus closes soon after birth, and somewhat later a velum closes the foramen ovale.

Frequently, in atresia of the aortic valve, there is an associated anomaly (such as a septal defect), together with a widely patent ductus arteriosus. The latter occurred in this case, but there was no auricular or ventricular septal defect. It is also common in this group of defects which cause cyanosis to find the most severe type of congenital lesion. This results from the fact that there is no satisfactory collateral circulation except through the patent ductus arteriosus. Consequently, it is usual to find clinical evidences of marked cyanosis and a very considerable degree of dyspnea. However, in this case these features were entirely absent.

To understand why no cyanosis nor dyspnea appeared, it is necessary to visualize the exact method of circulation in this case. The oxygenated blood did, as in the normal fetal circulation, reach the left auricle and then proceed into the left ventricle. It could not be pumped by the left ventricle into the aorta because the valve of the latter was completely occluded. Actually, an eddy was probably set up and the blood swirled around in the left ventricle and back into the left auricle. Here some blood may, by back pressure, have been forced into the pulmonary veins. Thus the oxygenated blood that normally passes through the foramen ovale from the right auricle into the left heart and then into the aorta was in this case prevented from so doing by the atretic aortic valve. Hence the left heart was only a blind pocket which received a small current of blood, and the left ventricular systole prevented stasis and subsequent thrombus formation.

The oxygenated blood from the inferior vena cava had to mix with the more venous blood of the superior vena cava, which also entered the right auricle. The mixture passed into the right ventricle and on through the ductus arteriosus into the arch of the aorta and systemic circulation. It is to be assumed that this free mixing of the arterial and venous blood accounted for the absence of cyanosis. The aortic valve lesion cannot be regarded as the result of an acquired infection.

SUMMARY

These are the features of the case:

1. Congenital atresia of the aortic valve, which was a developmental defect of unknown etiology.

2. Complete absence of clinical signs of congenital heart disease.

3. A hypoplastic left ventricle with an endocarditis throughout the chamber.

4. Aortic atresia, shown to be very rare in a series of thirty-five congenital heart anomalies collected at the McGill Pathological Institute. Aortic stenosis is far more common. Still more frequent are interventricular septal defects, many of which are associated with incomplete rotation of the great vessels on the heart.

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Department of Reviews and Abstracts

Selected Abstracts

Gregg, Donald E., and Dewald, Donald: The Immediate Effects of the Occlusion of the Coronary Veins on the Dynamics of the Coronary Circulation. Am. J. Physiol. **124**: 444, 1938.

The phasic changes in venous pressure, peripheral coronary pressure, and arterial inflow in the heart have been studied by optical methods before and after acute cardiac venous ligation (coronary sinus or great cardiac vein).

The intravenous pressure rises from control values of about 10/2 mm. Hg to figures which during systole approach or exceed the aortic systolic and which rise in diastolic value to 20 to 40 mm. Hg.

The peripheral coronary pressure, simultaneously recorded, is elevated in the left coronary in like degree and has a contour and time relation similar to the venous pressure, although its ordinate values are generally slightly less. Probable explanations for these changes in venous and peripheral coronary pressure are advanced.

The arterial inflow into the left coronary is reduced considerably, while that into the right coronary is presumably not affected. Since, however, the left coronary inflow does not approach zero and the myocardium still contracts, it is believed that there are potent drainage channels still remaining. These are presumably venous, since if a left coronary ramus is now occluded the myocardium fails to contract even if the peripheral coronary is allowed to bleed.

Since it has been found that acute cardiac venous ligation does not prevent failure of contraction in a myocardial area whose coronary has been ligated and does reduce materially the left coronary arterial inflow, such a procedure cannot be regarded as a method of choice for encouraging the blood supply to such a potentially infarcted area.

AUTHORS.

Chen, K. K., Robbins, E. Brown, and Worth, Harold: The Significance of Sugar Component in the Molecule of Cardiac Glycosides. J. Am. Pharm. A. **27**: 189, 1938.

The potency of five cardiac aglycones (strophanthidin, digoxigenin, digitoxigenin, calotropagenin and scillaridin A) has been carefully determined.

Each aglycone is less powerful on the heart than its parent glycoside—more pronounced in frogs than in cats. If the aglycone undergoes chemical changes during hydrolysis, as in the case of scillaridin A and calotropagenin, the cardiac action is reduced much further.

The emetic action of strophanthidin, digoxigenin and digitoxigenin, on the other hand, is greater than that of cymarin, digoxin and digitoxin, respectively, molecule for molecule. When the structure of the aglycone is modified during hydrolysis, such as calotropagenin, the emetic action is diminished, but not to the same extent as the cardiac action.

The persistence of action among the aglycones is slight; that is, they are all rapidly eliminated from the circulation. This is particularly true with digitoxigenin in contrast with digitoxin.

Digitoxigenin caused a brief initial stimulation as manifested by convulsions, followed by marked depression of the central nervous system in cats and frogs. Digitoxin has no such action in corresponding doses.

AUTHORS.

Stead, Eugene A., Jr., and Kunkel, Paul: A Plethysmographic Method for the Quantitative Measurement of the Blood Flow in the Foot. J. Clin. Investigation **17**: 711, 1938.

A plethysmographic method has been described for the quantitative measurement of the blood flow in the foot. With a standard correction for the inertia of the plethysmograph-bellows system, the instrumental error was found to be ± 3 per cent. The plethysmograph is also useful in the study of the vasomotor reactions of the vessels of the foot.

AUTHORS.

Nylin, S., and Sällström, T.: Three Synchronised Leads Between Fixed Points on the Heart Projection in the Chest Wall. Acta med. Scandinav. **96**: 1, 1938.

A study of chest leads was made according to the Wood-Wolferth technique and needle electrodes. The electrodes were placed in certain locations determined after x-ray examination of the heart. In normal persons they found the chest leads remarkably constant. In cases of acute coronary occlusion and of coronary disease changes were found which were consistent with those published in the American literature.

JENSEN.

Bock, H.: The Q-T Interval in Diphtheria Affecting Children. Ztschr. f. Kreislaufforsch. **30**: 761, 1938.

Twelve hundred electrocardiograms on 300 diphtheria patients were studied. It was found that the Q-T interval lengthened in diphtheria. This gives evidence of myocardial involvement. Extreme prolongation is a sign of bad prognosis.

KATZ.

Damin, Bustave J., and Moore, Robert A.: Cardiac Muscle in Idiopathic Hypertrophy of the Heart in Infancy and in Normal Growth. Arch. Path. **27**: 122, 1939.

In a case of idiopathic hypertrophy of the heart in an infant 53 days old the apparent number of muscle fibers was increased above the normal, but there was no increase in the number of nuclei.

A study of the hearts of an infant 2 months old, a child 8 years old, and an adult indicates that there is an increase in the total number of fibers and in that of nuclei during normal growth.

AUTHORS.

O'Farrell, P. T.: The Clinical Diagnosis of Congenital Heart Disease. Irish J. M. Sc. **153**: 597, 1938.

The author discusses the clinical signs and diagnosis of congenital lesions of the heart which are compatible with life, and which present fairly distinct clinical or radiologic features. The approach to the clinical diagnosis should follow a definite

plan. The first step which may be relatively easy is to establish the existence of a congenital lesion by ruling out the possibility of acquired disease. The next step, which is much more problematical, is to define the precise anatomic lesion or lesions. In the majority of cases only an approximate diagnosis can be attempted. There are certain criteria which are extremely helpful and he discusses these, each briefly.

There is also a discussion of each of the common clinical types of lesions with the symptoms and signs usually associated with each one.

Altogether, the article presents a most interesting and intelligent review of this subject.

McCULLOCH.

Bell, G. H.: The Human Foetal Electrocardiogram. J. Obst. & Gynaec. Brit. Emp. **45**: 802, 1938.

Using a thermionic valve electrocardiograph, capable of very high amplification, the electrocardiograms obtained when leads are taken from the abdomen of pregnant women show in some cases waves which are almost certainly fetal in origin. The evidence supporting the fetal origin is that the direction of the fetal deflection depends on the presentation (vertex or breech) and in a case of a twin pregnancy two sets of deflections were obtained.

Of thirty-three cases examined in the last two months of pregnancy about one-third showed positive results, but the other two-thirds did not show any wave on the electrocardiogram which could be definitely recognized as fetal.

It is suggested that the failure to secure positive results in all cases is due partly to differences in the electrical properties of the abdominal wall, and partly to the electrical disturbances produced by the abdominal muscles, and not to insufficient sensitivity of the apparatus or to differences between the fetuses.

AUTHOR.

Coburn, Alvin F., and Pauli, Ruth H.: The Significance of Prolonged Streptococcal Antibody Development in Rheumatic Fever. J. Clin. Investigation **18**: 141, 1939.

Findings are presented which support the view that prolonged increases in streptococcal antibody, such as are observed in rheumatic fever, signify subclinical activity of hemolytic streptococcus.

AUTHORS.

Westphal, K., and Sievert, C.: Concerning the Stimulating Material of Genuine Hypertension. Ztschr. f. Klin. Med. **133**: 223, 1937-38.

1. Endocrine disharmony in genuine hypertension—the occasion to hunt for and to find the stimulative material (p. 223): A number of patients who exhibit "genuine hypertension" associated with a variety of the stigmas of endocrine disturbances are described. They fall, chiefly, into two groups: adolescents with dystrophia adiposogenitalis; and middle-aged obese men with feminine habitus and loss of libido. They note, also, that when two of the adolescent cases without hypertension were treated with pituitary (hypoloban) and thyroid extract, they developed a hypertension. Finally, analysis of 100 cases of hypertension revealed some evidence of endocrine disturbance in all but eleven instances.

These observations led them to look for a pressor substance in the blood of hypertensive patients by the method of Anselmino and Hoffmann (ultrafiltration). A substance was found which regularly gave a rise in arterial pressure of rabbits on intramuscular injection, which persisted usually for as long as an hour.

2. Results of the study of pressor substances in the blood of genuine, renal, and malignant hypertension (p. 248): The pressor substance was found present in all but 15 of 102 instances of "genuine hypertension" in about the same proportion of cases with malignant sclerosis and in about half of those with acute nephritis. Several instances are recorded wherein the amount of pressor substance varied with the level of blood pressure.

3. The technique of demonstrating the pressor substance, its physicochemical properties as well as proof of the cortico-tropic substance (p. 261): The substances resembles Tonephin (posterior pituitary Extract I-g. Farbenindustrie A.-G.) in some ways (destroyed easily by alkali and ultraviolet light) but differs in others (lacks antidiuretic action and is active intramuscularly). The authors seem to believe it to be similar. Besides the pressor action, two other actions of the ultrafiltrate were shown to be present by their effect upon the size and lipoid content of the adrenal gland—the first was found to be identical with the corticotropic hormone of the anterior pituitary and the second was thought to be similar to the adrenal-tropic hormone.

4. Studies concerning the circulatory action of the pressor substance from the blood of genuine hypertension (p. 277): The pressor effect is shown to be peripheral in action.

5. Studies concerning the acute influence of the pressor substance upon blood pressure, adrenal secretion, and chronic studies of blood pressure (p. 291): Daily injections of the ultrafiltrate of blood from hypertensive patients give rise to chronic hypertension and increased lipoid content of the adrenal glands in rabbits. Neither of these phenomena occurs when the ultrafiltrate is obtained from normal blood. A single injection gives rise to a hyperglycemia which persists for seven or eight hours and which is abolished by removal of the adrenal glands.

The symbiosis of the cortex and medulla of the adrenal from the point of view of histological studies of the adrenals under different experimental and pathological conditions and especially in genuine hypertension (p. 311).

6. From histologic studies of adrenals in experimental and "genuine" hypertension, the conclusion is reached that both medulla and cortex are affected.

7. Genuine hypertension as a primary endocrine disease (p. 342). Three patients with hypertension were subjected to removal of one adrenal gland and implantation of three calves' hypophyses. Level of blood pressure for all three fell promptly but the records show only a few weeks of postoperative follow-up examinations. Also several patients with circulatory collapse (pneumonia, etc.) and chronic hypotension were treated with whole blood (transfusions) or ultrafiltrate of blood from hypertensive patients with rise in arterial pressure and increase in general strength.

From this series of studies the authors conclude that hypertension is primarily an endocrine disturbance.

STEELE.

Williams, John R., Jr., Wegria, R., and Harrison, T. R.: Relation of Renal Pressor Substance to Hypertension of Hydronephrotic Rats. Arch. Int. Med. **62**: 805, 1938.

Rats with spontaneous bilateral hydronephrosis display well-marked elevation of blood pressure. Rats with spontaneous unilateral hydronephrosis may or may not have an elevated blood pressure. Hydronephrotic rats respond to the injection of renal extract with a more marked rise in blood pressure than do normal rats of similar size and age. Extract of the abnormal kidneys of rats with spontaneous unilateral hydronephrosis produces greater pressor effects than does a similar extract of the normal kidneys of the same rats. Extract of the kidneys of rats with spontaneous bilateral hydronephrosis causes a greater rise in blood pressure than does extract of the kidneys of normal rats.

Ligation of one ureter for a period of several days causes slight hydronephrosis but no constant rise in blood pressure. After unilateral ureteral ligation the sensitivity of rats to renal pressor substance is somewhat greater than that of normal animals. Extract of the kidney rendered hydronephrotic by ligation of the ureter has a greater pressor effect than does a similar extract of the opposite normal kidney of the same animal. AUTHOR.

Langendorf, R., and Pick, A.: On the Diagnosis of Myocardial Infarct With the Aid of Chest Wall Leads. Acta med. Scandinav. **96**: 80, 1938.

Little work has been done on the reappearance of the preintrinsic positive deflection in chest leads following posterior coronary occlusions. There have been discussions of the negative deflection which frequently precedes the preintrinsic positive deflection. Most authors consider that such a deflection, if big, has a similar significance as has absence of the preintrinsic posterior deflection. Normally this wave is always less than 0.3 millivolt. When it becomes greater than this, the authors consider it of great diagnostic importance. Often, however, it is important to change the position of the pick-up electrode to various areas between the apex and the left sternal border. Sometimes the preintrinsic position deflection returns before the T-wave changes return to normal. Sometimes it is present, though small, in the presence of large infarcts. This fact somewhat impairs the value of the chest lead. Differences in curves originating from different sites of application of electrodes are brought about by the use of large electrodes. AUTHORS.

Schwab, Edward H., and Curb, Dolph L.: A Note on the Diagnosis of Hypertensive Cardiovascular Disease Without Hypertension. J. Lab. and Clin. Med. **24**: 125, 1938.

The middle-aged patient who presents moderate to marked cardiac enlargement and who does not have hypertension or significant vascular lesions provides an interesting diagnostic problem from the etiological standpoint. The cause of the cardiac enlargement in these patients is usually obscure. O'Hare and his associates have emphasized that under such circumstances the patient probably has had a previous hypertension. Although it is probable that hypertension has been present in such patients, a definite history of this is usually difficult to confirm. It was considered that these suspected hypertensive cardiopaths might still retain the hypersensitivity of the vasomotor apparatus to stimulation even though their blood pressure was no longer elevated. The cold pressor test of Hines and Brown was utilized in testing the vasomotor reactivity of these patients. Seven subjects with known previous hypertensive vascular disease in whom the blood pressure had fallen to normal or subnormal were subjected to the cold pressor test. Five of the seven patients gave a marked hypertensive type of response. One gave a borderline type of response and one an essentially normal response. In the patient with the borderline response it was felt that a primary nephritis might have been the etiological factor of the hypertension. The findings in this small group suggest that the application of the cold pressor test to patients of this type would materially aid in clarification of the etiological cardiac diagnosis. HINES.

Major, Ralph H.: Blood "Guanidine" in Arterial Hypertension: A Review of Eight Hundred Cases. Arch. Int. Med. **62**: 946, 1938.

The "guanidine" content of the blood of 800 patients with hypertension observed over a period of ten years was increased in 43 per cent of the entire series and in 32 per cent of those whose blood had a nonprotein nitrogen content not exceeding 40 mg. per 100 c.c. NAIDE.

Mills, John H., and Horton, Bayard T.: Clinical Aspects of Aneurysm. Arch. Int. Med. 62: 949, 1938.

A total of 596 cases of aneurysm were recorded at the Mayo Clinic in the years 1925 to 1935, inclusive. In this series of cases, 143 of the aneurysms were intracranial, 339 were intrathoracic, 80 were intra-abdominal, 21 involved the extremities, and 13 were of a miscellaneous character. Syphilis was present in 3.5 per cent of the cases of intracranial aneurysm, in 70 per cent of the cases of thoracic aneurysm, in 8.8 per cent of the cases of intra-abdominal aneurysm, in 9.5 per cent of the cases of aneurysm of an extremity, and in 7.7 per cent of the miscellaneous cases of aneurysm. In a total of 172, or 28.9 per cent, of the 596 cases the diagnosis of aneurysm was verified at operation or necropsy.

AUTHORS.

Boland, Edward W., and Willus, Fredrick A.: Changes in the Liver Produced by Chronic Passive Congestion. Arch. Int. Med. 62: 723, 1938.

The usual histopathologic picture of the liver in cases of prolonged or recurrent episodes of congestive heart failure is that of central lobular atrophy, or necrosis, or both. Condensation of reticulum and thickening may or may not be present.

The presence of condensation of reticulum alone does not warrant the use of the term cardiac cirrhosis.

True cirrhosis, developing in the course of congestive heart failure, does occur but is rare. No definite criteria were elicited from this study whereby the development or presence of cardiac cirrhosis can be recognized clinically.

AUTHORS.

Epstein, Bernhard S.: The Visualization of the Aorta by the Method of Roentgenographic Overpenetration. Am. J. Roentgenol. 40: 396, 1938.

The technique of overpenetration has been useful in outlining the cardiac shadow in patients with opacities in the adjacent lung fields. Extension of the heart shadow below the diaphragm may be demonstrated. Shadows of double density on the right cardiac border in instances where the left auricle approaches the right border are sometimes seen. The contour of the thoracic spine can be determined, and instances in which a thoracic deformity was of differential diagnostic import have been noted. It is also possible to visualize the trachea and main bronchi.

AUTHOR.

Grandgérard, R., and Heim de Balsac, R.: The Primary Arterial Tree of the Lungs and the Cortical Destination of Its Ramification. Presse méd. 45: 444, 1937.

Through visualization by Lucien's method the arterial tree in the lungs is subdivided into various sections. The notion of areas of ventilation of the lungs added to the knowledge of the elements of the distribution of vessels is useful in the localization of lesions of the lung even after projection on to the single plane of the x-ray film.

JENSEN.

Goldblatt, Harry: Experimental Observations on the Surgical Treatment of Hypertension. Surgery 4: 483, 1938.

The effect of experimental occlusion of the renal artery on the production of hypertension is reviewed and discussed.

The author then discusses the application of this observation to hypertension in humans. Whether renal decapsulation and other surgical procedures for the establishment of collateral circulation to the kidney would be effective in either essential hypertension or other types, must be worked out. The author believes there is probably more justification on an experimental basis for the surgical procedure than there has been for some of the others that have already been practiced. The cases in which the surgical production of accessory circulation would be most effective would be those in which the hypertension is due to sclerosis of the main renal arteries alone, or their very large branches. The difficulty of making a diagnosis of this condition is obvious so that unless the method could be applied to essential hypertension associated with renal arteriolar sclerosis, the procedure would be of greatly restricted value.

McCULLOCH.

Weitzmann, G.: (Abstracted From Notes.) Report of the Fourteenth Meeting of the German Pharmacological Society April 24 to 28, 1938. Ztschr. f. Kreislaufforsch. 30: 736, 1938.

P. Holtz, Greifswald: "Formation of a Pressor Substance From Dioxyphenylalanin by Animal Tissues." Kidney extract forms a pressor substance from dioxyphenylalanin when the medium is made anoxemic. The substance appears to be oxytyramin.

Rühl and Thaddea, Berlin: "Lactic Acid in the Heart-Lung Preparation Following Caffeine." Caffeine, 0.15-0.35 gm., makes the heart in the heart-lung preparation insufficient and at the same time lactic acid accumulates in the blood. This differs from other types of damage to the heart, viz., pernocton, histamine, or N_2 where no interference with lactic acid utilization is seen.

Kuschinsky, Berlin: "Water Balance." The quantity of antidiuretic hormone of the posterior pituitary gland was determined in male rats. Excess water (one-twentieth body weight daily for one week) was found to have no effect on this determination. When, however, 4 per cent NaCl was added, the hormone was decreased in amount on the day following. The same decrease was found to occur after novasurol, but theophyllin had no such effect.

Hildebrandt, Osterwald, Giessen: "Strophanthin on Coronary Flow." In the intact anesthetized animal, coronary flow was studied by means of a Rein stromuhr. It was found that doses of strophanthin equivalent to 0.15 to 0.5 mg. for man had no direct effect on coronary blood flow to the right coronary artery. The coronary flow changes following strophanthin paralleled the changes in peripheral flow.

Hahn, Cologne: "Digitalis Sensitivity When Blood Calcium Is Elevated." The lethal dose of strophanthin is decreased when blood calcium is raised by calcium chloride injections.

Hessel, Frankfort: "Experimental Observations on the Pathogenesis of Renal Hypertension." Injections of venous blood from the ischemic kidneys of animals (rabbit and dog) having developed chronic hypertension, cause a rise in pressure in the recipient animal. Arterial blood or venous blood from nonischemic kidneys does not have this action. Renin is the substance to which this pressor action is attributed. This material causes a decrease in renal flow and so can establish the mechanism whereby hypertension is established and maintained. Removal of the kidneys in animals rendered hypertensive by chronic injections of renin leads to a fall in blood pressure. Renin thus appears to be responsible for the vicious cycle of hypertension.

KATZ.

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